Registration No 11556-151 Vol. 2

Material Sent for Data Extraction

Reg. # 11556-151

Description: SPOT-ON INCIDENT DATA
6/2011 - 6/2013

☐ Material(s) Sent to Data Extraction Contractors:

- ☐ New Stamped Label Dated _____
- ☐ Notification Dated _____
- ☐ New CSF(s) Dated _____
- ☐ Other: _____

☐ Decision #: _____

☑ Other Action/Comments: SPOT-ON MITIGATION REQUIREMENTS

File this coversheet and attached materials in the jacket. It must be well organized and clipped together, NOT STAPLED. Then give the jacket with the coversheet and materials to staff in the Information Services Center (ISC) (Room S-4900). If a jacket is full or only available as an image, please file materials in a new jacket and bring it down to the (ISC). For further information please call 703-605-0716.

Reviewer: KAITLIN KELLER

Phone: 308-8172 Division: RD

Date: 6/18/2013

Bayer HealthCare
Animal Health

Via Federal Express - Express Saver

December 9, 2010

Document Processing Desk
Office of Pesticide Programs (7504P) – NonPRIA
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Attention: Ms. Venus Eagle/PM 01

Subject:

Advantage II Kitten (EPA Reg. No. 11556-150)
Advantage II Small Cat (EPA Reg. No. 11556-151)
Advantage II Large Cat (EPA Reg. No. 11556-152)

Bayer HealthCare LLC
Animal Health
P.O. Box 390
Shawnee Mission, KS 66201-0890

Dear Ms. Eagle:

Reference is made to the current registrations of the subject products. One of the conditions of acceptance of the subject registrations is that "[We] must provide the Agency with a projected release for shipment at least 30 days in advance."

Therefore, we are hereby notifying the Agency that our first anticipated shipment of product will be on or after January 17, 2011.

If you have any questions, please do not hesitate to call (913-268-2751).

Sincerely,

Douglas A. Spilker, Ph. D.
Manager, EPA Regulatory Affairs
Doug.Spilker@Bayer.com

Cc: K. Davis (EPA) – email

Bayer HealthCare

May 29, 2013

Document Processing Desk
Office of Pesticide Programs (7504P) – NonPRIA
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Attention: Ms. Venus Eagle/PM01

Bayer HealthCare LLC

Animal Health

P.O. Box 390
Shawnee Mission, KS
66201-0390

Subject: Advantage II Kitten (EPA Reg. No. 11556-150)
Advantage II Small Cat (EPA Reg. No. 11556-151)
Advantage II Large Cat (EPA Reg. No. 11556-152)
Advantage II Small Dog (EPA Reg. No. 11556-128)
Advantage II Medium Dog (EPA Reg. No. 11556-125)
Advantage II Large Dog (EPA Reg. No. 11556-127)
Advantage II Extra Large Dog (EPA Reg. No. 11556-130)

Please find enclosed a new format for the conditional registration requirement of the enhanced quarterly incident report for Advantage II Dog and Cat registrations for the quarter starting January 1, 2013.

This submission includes the following tables covering incident reporting from January 1, 2013 through March 1, 2013 by brand:

Incident Count by Severity Code and Route of Exposure: Canine, Feline, Human
Summary for ALL Species
Secondary Exposure Incident Count
Summary for ALL Species
Incident Count by Severity Code and Age
Incident Count by Severity Code and Weight
Incident Count by Breed
Summary for ALL Species
Incident Count by Clinical Sign-Summary

To provide the Agency the ability to sort, this data is being provided electronically on a CD. The data was extracted from Bayer's pharmacovigilance data base (P.V. Works).

Deaths:

Advantage II for Cats Deaths Reports with a Date First Valid between 01 Jan 2013 and 31 Mar 2013 Inclusive:

2013-US0000079

Summary:

On approximately 01-Jan-2012, a 18 year old, 16.0 pound, neutered, male, Domestic Shorthair feline, in fair condition, with a history of a urinary tract infection, was administered 1 tube of Advantage II Large Cat (Imidacloprid-Pyriproxyfen) once topically by the owner. Approximately during Feb 2012 the cat had weight loss, urinary and bowel incontinence, and vocalization. On 03-Mar-2012 the cat was examined by a veterinarian and no medical treatments were performed and the cat was euthanized.

Assessment:

The clinical signs reported are not consistent with a topically acting product. Euthanasia is never expected following the use of any topical product. No necropsy was performed and the body has already been taken care of. Without a necropsy, it is impossible to determine what other disease process played a part in the animal's death. No quality issues were noted upon product investigation.

2013-US0000716

Summary:

On an unknown date in approximately 2011, a 2 year old, 5 pound, intact, male, Domestic Shorthair feline, in good condition, with no known concomitant medical condition, was administered 1 tube of Advantage II Large Cat (Imidacloprid-Pyriproxyfen) once topically by the owner. Immediately post application the cat was tachypneic and hyperactive and the clinical signs resolved approximately 3 hours later. Did not apply the product for a period of 1 year approximately, at whicb time the cat was badly injured on a fence and developed a severe infection in one leg. Shortly after this, the cat was found dead. No necropsy was performed.

Assessment:

This patient died over a year following exposure to the product, and an injury resulted in a severe infection. The product was used in an off label manner and was overdosed. The signs resolved rapidly and without medical intervention. The owner originally called Bayer with questions about partial doses for Advantage II and not to report this event. Due to the medical condition that the cat developed one year after the product was applied it is unlikely that the medications played a role in the outcome of this case.

2013-US0000777

Summary:

On approximately 09-Sep-2012, a 10 year old, unknown signalment feline, in unknown condition, with no known concomitant medical condition, was administered 1 tube of Advantage II Small Cat (Imidacloprid-Pyriproxyfen) once topically by the owner. Approximately on 09 Oct 2012 the cat died. The vet was suspecting of cardiac failure.

Assessment:

Death is never expected following the use of any topical product. No necropsy was performed and the body has already been taken care of. Without a necropsy, it is impossible to determine what other disease process played a part in the animal's

death.
The owner originally called Bayer with for a different reason and not to report this event. The owner mentioned that the vet suspected of heart failure.

2013-US0001683
Summary:
On an unknown date, an 11.5 year old, 13 pound, neutered, male, Unknown Breed feline, in good condition, with no known concomitant medical conditions, was administered 1 tube of Advantage II Large Cat (Imidacloprid-Pyriproxyfen) once topically by the owner. An undetermined time after application the cat was examined by a veterinarian and diagnosed with acute renal failure. On approximately 01-Feb-2012 the cat was humanely euthanized. No necropsy was performed.

Assessment:
This is a topical acting product and would not expect to see any systemic abnormalities. This patient was diagnosed with acute renal failure and was humanely euthanized following diagnosis. Reporting party contacted BVTS exclusively to inquire about use of the product in another animal.

2013-US0002208
Summary:
On approximately 01Sep2011, a 14 year old, feline of unknown signalment, in unknown condition, with no known medical conditions, was administered 1 tube of Advantage II Small Cat (Imidacloprid-Pyriproxyfen) once topically by the owner. On approximately 01Sept2012, the cat passed away.

Assessment:
The symptom observed is not anticipated following use of this product. It is unknown what, if any, medical conditions the cat had prior to application of the product. No necropsy was performed. No quality issues were noted upon product investigation.

2013-US0002646
Summary:
On approximately 01-Jan-2012, a female, feline, of unknown signalment, in unknown condition, with no known concomitant medical conditions, was administered 1 tube of Advantage II (cat-unspecified) (Imidacloprid-Pyriproxyfen) once topically by the owner. On approximately 15-Jan-2012, the patient became pruritic. An unspecified amount of time later, the owner switched the patient to firponil / s-methoprene and the pruritus resolved. An unspecified amount of time after that, the patient died.
Assessment:
The reported signs are not anticipated following the use of this product. Numerous other factors could cause pruritus, so that should be considered.

2013-US0002929
Summary:
On approximately 01Apr2011, an 7 year old, feline of unknown signalment, in unknown condition, with no known medical conditions, was administered 1 tube of Advantage II Large Cat (Imidacloprid-Pyriproxyfen) once topically by the owner. On approximately 01Apr2012, the cat passed away, possibly from a stroke.

Assessment:
The symptoms observed are not anticipated following use of this topically-applied product. It is unknown what, if any, medical conditions, the cat had at the time the product was applied. The cat was not examined by the veterinarian and no necropsy was performed. Other etiologies must be considered. The purpose of call for the reporting party was to ask about the expiration of the product, whether or not it could be used on her new pet, and not to report the death of her previous cat. No quality issues were noted upon product investigation.

2013-US0005318
Summary:
On approximately 01Nov2012, a 15 year old, 15 pound, neutered, male, Domestic Shorthair feline, in unknown condition, with an active flea infestation was administered 1 tube of Advantage II Large Cat (Imidacloprid-Pyriproxyfen) once topically by the owner. Approximately 05Nov202 the patient developed application site alopecia. The hair grew back by approximately 26Nov2012. Approximately 18Feb2013 the patient passed away due to the development of cancer.

Assessment:
Application site alopecia may occur with any topically applied product. Considering the short time to onset and the location of the alopecia, the patient may have had an individual sensitivity to the product. The hair grew back within a few weeks without further complications. Cancer leading to death would not be typical with proper use of the topically active product. Cancer in a 15 year old pet is not uncommon. Product involvement is not likely. The intent of the phone call was to report the application site alopecia, not the death of the patient.

2013-US0005751
Summary:
On an unknown date in Sep2012 a feline of unknown signalment, in unknown condition with no known concomitant medical conditions, was administered 1 tube of Advantage II Large Cat (Imidacloprid-Pyriproxyfen) once topically by the owner. On an unknown date in Sep2012 the cat was hit by a car and subsequently died.

Assessment:
The owner initially contacted Bayer Animal Health to seek advise on how to control an active flea infestation on another pet and not to report the death of this pet. Due to patient history of being hit by a car, it is very unlikely that the product has any relation to the patient's death.

2013-US0007117
Summary:
On approximately 18Jan2013, a 2 year old, 7.5 pound, neutered, male, Domestic Longhair feline, in good condition with no known concomitant medical conditions, was administered 1 tube of Advantage II Large Cat (Imidacloprid-Pyriproxyfen) once topically by the owner. This product was used in off label manner and is considered an over dose for this patient. On approximately 28Jan2013 the cat was irritable (behavioral). On approximately 02Mar2013 the cat was regurgitating. On approximately 07Mar2013 the cat was seen by a veterinarian for abnormal breathing. On approximately 14Mar2013 the cat was seen by another veterinarian for a second opinion due to ongoing clinical signs and weight loss. Radiographs

were taken and identified fluid on the chest and abnormal appearances within the thorax, no specifics provided. On approximately 15Mar2013 the cat was having difficulty swallowing. The cat was hospitalized and fluid was drained from the chest and the cat was placed on oxygen. On 19Mar2013 the cat was not improving and was euthanized per the owner's request. A necropsy or analysis of chest fluids were not performed.

Assessment:
The product was used in an off label manner and was an over dose for this cat. Due to the long duration of the time to onset of this patient's clinical signs from when the product was used, it is very unlikely that the product has any relation to the patients illness. No necropsy was performed and the body has already been taken care of. Without a necropsy, it is impossible to determine what other disease process played a part in the animal's illness.

Advantage II for Dogs Deaths Reports with a Date First Valid between 01 Jan 2013 and 31 Mar 2013 Inclusive

2013-US0000528
Summary:
On approximately 01Jan2012, a canine of unknown signalment, in unknown condition, with no known medical conditions, was administered 1 tube of Advantage II Extra Large Dog (Imidacloprid-Pyriproxyfen) once topically by the owner. An undetermined amount of time later, the dog passed away due to old age.

Assessment:
The symptom observed is not anticipated following use of this topically-applied product. It is unknown what, if any, medical problems the dog had at the time of product application. As the owner reports the dog passed away of old age, other etiologies must be considered and product relation has been deemed unlikely. No necropsy was performed.

2013-US0000640
Summary:
On 05-Jan-2013, an 11 month old Rottweiler canine, in good condition, that was bred during her first heat cycle and currently pregnant and ready to begin whelping, was administered 1 tube of Advantage II (dog unspecified) (Imidacloprid/ Pyriproxyfen) of an unknown size once topically route by the owner. 13 hours post application the bitch began whelping at her expected delivery time. The first pup was stillborn (stillborn pup was sharing a sac with another pup) and she delivered 13 pups total within the next 5 hours. Approximately 19 hours post application, after the pups had attempted to nurse, the 12 pups began vocalizing and 6 passed away. The owner took the remaining 6 pups to the veterinarian. All of the pups had very low temperatures and were dehydrated. One of the pups presented gasping for air and was immediately given oxygen but passed away within 5 minutes. 1 of the pups was gasping and was euthanized before receiving any treatments. 1 of them received subcutaneous fluids and oxygen but passed away approximately 5 minutes later. The other 3 pups were also administered subcutaneous fluids only as they were not having any breathing issues. The remaining 3 pups were sent home with the owner. Once home, 1 of the remaining 3 nursed on the mom and then, approximately 15 minutes later, passed away. The owner has continued to bottle feed the 2 remaining pups and both of the pups and the mom are asymptomatic.

Assessment:
This is not anticipated with the proper use of a topically applied product. The veterinarian believed the cause of the events to be more likely associated with the bitch being bred at a young age during her first heat cycle. No necropsy was performed and 2 of the pups have recovered from this event with minimal veterinary intervention.

2013-US0000888
Summary:
On approximately 01-Sep-2012, a 17 year old, 45 pound, neutered, male, Border Collie canine, in fair condition, with no specific medical conditions, was administered 1 tube of Advantage II Large Dog (Imidacloprid-Pyriproxyfen) once topically by the owner. An unknown amount of time post application the dog began having difficulty walking. On approximately 30-Sep-2012 the dog was euthanized for his continued declining health. No necropsy was performed.

Assessment:
This is not expected with the proper use of the product. It is not anticipated that any signs were associated with the use of the product and the dog had never had any previous reactions with the product. This is more likely associated with tbe age of the dog.

2013-US0001462
Summary:
On approximately 01-Oct-2011, a 20 year old, 64 pound, spayed, female, Mixed Breed canine, in fair condition, with no known concomitant medical conditions, was administered 1 tube of Advantage II (dog-unspecified) (Imidacloprid-Pyriproxyfen) once topically by the owner. An unspecified amount of time post application the dog began having neurological signs (unspecified). The owner continued to use the product seasonally and the neurological signs continued to worsen. On 24-Oct-2012 the owner had the dog euthanized due to the condition. No necropsy was performed.

Assessment:
This is not anticipated with the proper use of the product. The dog had used the product for an extended amount of time with no issue. The dog was an elderly dog and it is impossible to determine what, if any, role the product played in these events.

2013-US0001654
Summary:
On approximately 01-Jan-2010 a 10 year old, unknown weight, spayed, female, Maltese canine, in good condition, with no known concomitant medical conditions, was administered 1 tube of Adavntage (dog unspecified) once topically by the owner. The owner continued to apply the product on an nnknown basis yearly. On approximately 01-Mar-2010 the dog had difficulty breathing. The dog was examined by the veterinarian and diagnosed with chronic obstructive pulmonary disease. The veterinarian prescribed an unknown dose of prednisone and an unknown dose of theophylline at that time. These treatments were used as needed. On 07-Nov-2012 the patient was administered an unknown amount of moxidectin injectable by the attending vet. On 15-Jan-2013 the dog was administered a distemper/parvo vaccination, a lepto vaccination, and a flu vaccination by the

attending vet, and was prescribed neomycin/polymyxin B/dexamethasone drops to be applied to the eyes for conjunctivitis. The dog was also administered 1 tube of Advantage II Smal Dog (Imidacloprid-Pyrifroxyfen) once topically by the owner. On 16-Jan-2013 the dog was listless, vomiting, and had soft stool. The owner contacted the veterinarian who advised that the dog be examined but the owner declined. 2 hours later the owner contacted the veterinarian and adivsed that the dog was uncomfortable and again declined an exam. 3 hours later the owner called and advised bloody diarrhea and wanted to wait until the next morning to have her examined. On 17-Jan-2013 the dog was examined by the veterinarian. Radiographs showed a dense mass cranial to the right kidney and excess gas in the intra-intestinal area. A fecal was performed and was negative. 20 minutes later the dog collapsed with respiratory distress. The veterinarian administered .5cc of doxapram intramuscular and .3cc of epinephrine intramuscular. The dog was intubated. 5 minutes later the dog passed away. On gross necropsy performed by the veterinarian the dog was found to have hemorrhagic enteritis, an enlarged heart, and an adrenal gland tumor.

Assessment:
No quality issues were noted upon product investigation. The clinical signs are not consistent with a topically acting product. On gross necropsy the dog was found to have hemorrhagic enteritis, an enlarged heart, and an adrenal gland tumor. These are more likely to have caused the death of the patient.

2013-US0003380
Summary:
On 01-Sep-2012, a 18 year old, 10 pound*, Schnauzer/Poodle (Miniature) crossbred canine, in poor condition, with a concomitant medical condition of age related hearing loss, was administered 1 dose of Advantage II Small Dog (Imidacloprid-Pyriproxyfen) once topically by the owner. On 01 Oct 2012 the dog died of unknown causes.

Assessment:
Death is never expected following the use of any topical product. No necropsy was performed and the body has already been taken care of. Without a necropsy, it is impossible to determine what other disease process played a part in the animal's death.
The owner originally called Bayer to report an AE for a different dog and mentioned this event. The dog was 18 years old and the owner said that is death was age related.

2013-US0005133
Summary:
On approximately 01-Aug-2012, a 8 year old, 120 pound, neutered, male, Golden Retriever canine, in poor condition, with a inoperable mast cell tumor on its leg, was administered 1 tube of Advantage II (dog-unspecified) (Imidacloprid-Pyriproxyfen) once topically by the owner. The dog had been undergoing chemotherapy since approximately 01-Apr-2012. On approximately 15-Sep-2012, the mast cell tumor had increased in size and began blocking bloodflow to the leg. Euthanasia was elected by the owner and this was performed by the veterinarian. No necropsy was performed.

Assessment:
The signs exhibited by this dog are not product related, but related to its

concomitant medical condition. This dog has a mast cell tumor and was undergoing chemotherapy which was unsuccessful. The tumor had grown to a size that caused loss of blood flow to the dog's leg. The owner elected euthanasia. The caller contacted Bayer Animal Health to inquire about using the remainder of the product on their new pet and not to report this event.

2013-US0005242

Summary:

On approximately 01Aug2011, an approximately 13.5 year old, male, Chihuahua canine, in poor condition, was administered 1 tube of Advantage II (dog-unspecified) (Imidacloprid-Pyriproxyfen) once topically by the owner. Concomitant Medical Conditions: inbred; brain tumor; liver issues; epilepsy. On approximately 01Aug2012, the dog developed seizures which continued, so the owner elected to euthanize the dog.

Assessment:

The patient had numerous serious concomitant medical conditions prior to product application. The subsequent euthanasia was likely related to complications from those ongoing medical issues rather than the application of the product. Therefore, other etiologies must be considered as product involvement has been deemed unrelated.

2013-US0005257

Summary:

On 01Mar2013, an 8 year old, 8.00 pound, neutered, male, mixed breed canine, in good condition, with an active flea infestation, was administered 1 tube of Advantage II Small Dog (Imidacloprid-Pyriproxyfen) once topically by the owner. 02Mar2013 the patient was found deceased. A gross necropsy was performed and the patient was found to have an enlarged heart. No other abnormalities were noted.

Assessment:

The exact cause of death of the patient in this case was not determined. Upon necropsy examination, it was determined the patient had cardiomegaly. It is well known that cardiac disease my lead to sudden death in patients. No quality issues were noted upon product investigation. The attending veterinarian did not believe the patient's death to be related to the administration of product.

2013-US0005606

Summary:

On approximately 01-Aug-2012, a 14 year old, male, Mixed Breed canine, in unknown condition with no known concomitant medical conditions, was administered 1 tube of Advantage II Extra Large Dog (Imidacloprid-Pyriproxyfen) once topically by the owner. On 18-Dec-2012, the dog passed away at home. The owner had not applied product during the winter months. A necropsy was not performed.

Assessment:

Since limited information was provided in this event, it is unknown what, if any, role the product had in this event. Due to the 3 month duration of the time between the last product application and death, product involvement is very unlikely. No product quality issues were found in the product investigation. The initial purpose of the owner contacting Bayer animal Heath was to inquire about the use of this product for use on a different pet and not to report this event.

We believe this summary of data meets the requested information in the Agency's requirements for enhanced reporting as outlined in its January 19, 2011 communication to Bayer.

A report with the confidential sales information and additional analysis of incident rates based on doses sold is being sent to the Registration Division, Immediate Office (attn. Ms. Kimberly Nesci).

If there are any questions regarding this submission, please contact me by phone at 913.268.2082 or by e-mail at jill.bodamer@bayer.com.

Jill Bodamer
Specialist
Regulatory Affairs

EPA Summary Report

Cases first valid from: 01-Jan-2013 to: 31-Mar-2013

Parameters:
For Brand : Advantage II Medium Dog

Incident Count by Severity Code and Route of Exposure

Species: Canine

		Route of Admin	
		Oral	Other
EPA Classification	D-B [Life threatening &/or resldual disabilit	*0*	*2*
	D-C [Non-life threat. pronounced symptoms	*0*	*11*
	D-D [Minimal symptoms (skin, eye or resp)	*1*	*34*
	TOTAL	**1**	**47**

Species: Feline

		Route of Admin
		Other
EPA Classification	D-D [Minimal symptoms (skin, eye or resp)	*1*
	TOTAL	**1**

Species: Human

		Route of Admin
		Other
EPA Classification	H-D [Minimal symptoms (skin, eye, or resp)	*1*
	TOTAL	**1**

Summary for ALL Species

		Route of Admin	
		Oral	Other
EPA Classification	D-A [Death]	*0*	*0*
	D-B [Life threatening &/or residual disability]	*0*	*2*
	D-C [Non-life threat. pronounced symptoms, no disability]	*0*	*11*
	D-D [Minimal symptoms (skin, eye or resp) resolved rapidly]	*1*	*35*
	D-E [Symptoms unknown or not specified]	*0*	*0*

		Route of A...n	
		Oral	Other
EPA Classification	G-A [Water Contamination - see guidelines]	0	0
	G-B [Water Contamination - see guidelines]	0	0
	G-C [Water Contamination - see guidelines]	0	0
	H-A [Person Died]	0	0
	H-B [Life threat. ,repro effects, &/or residual disability]	0	0
	H-C [Non-life threat. pronounced symptoms, no disability]	0	0
	H-D [Minimal symptoms (skin, eye, or resp) resolved rapidly]	0	1
	H-E [Symptoms unknown, unspecified or "delayed or chronic"]	0	0
	ONT [Other Non-Target Organisms]	0	0
	P-A [Plant - >45% of acreage exposed]	0	0
	P-B [Plant - <45% of acreage exposed]	0	0
	PD-A [Alleged damage that could have caused human injury]	0	0
	PD-B [Alleged to have caused damage >$5,000]	0	0
	PD-C [other allegations not in PD-A or B]	0	0
	W-A [Fish or Wildlife - see EPA guidelines]	0	0
	W-B [Fish or Wildlife - see EPA guidelines]	0	0
	TOTAL	**1**	**49**

NB: Counts reflect the numbers of doses for cases with EPA products - these may differ from the number of distinct case reports.
(Data columns which return no values are suppressed).

Secondary Exposure Incident Count

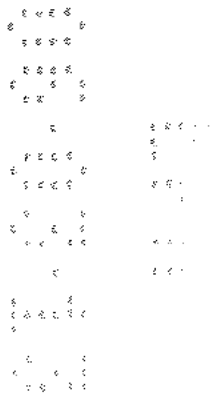
Species: Feline	Incident Count
Feline	1
TOTAL	1

Species: Human	Incident Count
Human	1
TOTAL	1

Summary for all Species

	Incident Count
Feline	1
Human	1
TOTAL	2

NB: Counts reflect the number of products having secondary exposure - these may differ from the number of distinct case reports



Incident Count by Severity Code and Age

Age Category	EPA Classification				
	D-B	D-C	D-D	H-D	Unassessed
<3 months	0	0	1	0	0
3-6 months	0	0	0	0	0
6-9 months	0	0	2	0	0
9-12 months	0	0	1	0	0
1 year	0	1	1	0	0
2 years	1	0	4	0	0
3 years	0	0	5	0	0
4 years	0	0	4	0	0
5 years	0	3	4	0	0
6 years	0	1	1	0	0
7 years	0	0	4	0	0
8 years	1	1	3	0	0
9 years	0	2	2	0	0
10 years	0	1	0	0	0
11 years	0	0	1	0	0
12 years	0	1	1	0	0
13 years	0	0	0	0	0
14 years	0	0	1	0	0
15 years	0	0	0	0	0
> 15 years	0	0	0	1	0
not specified	0	1	1	0	0
TOTAL	2	11	36	1	0

NB: Counts reflect the number of patients for cases with EPA products - these may differ from the number of distinct case reports.
(Data columns which return no values are suppressed).

Incident Count by Severity Code and Weight

		EPA Classification			
		D-B	D-C	D-D	H-D
Weight Category	< 11lbs	*0*	*2*	*8*	*0*
	11 - 16lbs	*0*	*5*	*13*	*0*
	16 - 20lbs	*1*	*2*	*8*	*0*
	> 20lbs	*0*	*2*	*7*	*0*
	not specified	*1*	*0*	*0*	*1*
	TOTAL	2	11	36	1

NB: Counts reflect the number of patients for cases with EPA products - these may differ from the number of distinct case reports. (Data columns which return no values are suppressed).

Incident Count by Breed

Species: Canine		Incident count
Breed	Mixed Breed (Canine)	11
	Chihuahua	7
	Shih Tzu	6
	Terrier (Jack Russell)	4
	Fox Terrier	3
	Poodle (Miniature)	3
	Unknown Breed (Canine)	2
	Cairn Terrier	1
	Chinese Crested	1
	Dachshund	1
	Dachshund (Miniature)	1
	German Shepherd Dog	1
	Maltese	1
	Pomeranian	1
	Pug	1
	Schnauzer (Miniature)	1
	Terrier (Rat)	1
	Yorkshire Terrier	1
	Yorkshire Terrier & Poodle (Miniature)	1
	TOTAL	**48**

Species: Feline		Incident count
Breed	Domestic Shorthair	1
	TOTAL	**1**

Species: Human		Incident count
Breed	Unknown	1
	TOTAL	**1**

Summary for ALL Species

		Incident count	
Species	Canine	*48*	96%
	Feline	*1*	2%
	Human	*1*	2%
	TOTAL	*50*	100%

NB: Counts reflect the number of patients for cases with EPA products - these may differ from the number of distinct case reports

Incident Count by Clinical Sign - Summary

System Organ Class	Incident Count	
Skin and appendages disorders	*44*	40%
Behavioural disorders	*17*	15%
Systemic disorders	*14*	13%
Digestive tract disorders	*8*	7%
Neurological disorders	*6*	5%
Application site disorders	*4*	4%
Musculoskeletal disorders	*4*	4%
Unknown	*4*	4%
Eye disorders	*3*	3%
Respiratory tract disorders	*3*	3%
Ear and labyrinth disorders	*1*	1%
Immune system disorders	*1*	1%
Reproductive system disorders	*1*	1%
GRAND TOTAL:	*110*	

NB: Counts reflect number of signs for cases with EPA products - these may differ from the number of distinct case reports

Validation Report

EPA Summary Report

Cases first valid from: 01-Jan-2013 to: 31-Mar-2013

Parameters:
For Brand : Advantage II Large Dog

Incident Count by Severity Code and Route of Exposure

Species: Canine

		Route of Admin
		Other
EPA Classification	D-A [Death]	1
	D-B [Life threatening &/or residual disabilit	3
	D-C [Non-life threat. pronounced symptoms	6
	D-D [Minimal symptoms (skin, eye or resp)	26
	TOTAL	36

Species: Feline

		Route of Admin
		Other
EPA Classification	D-C [Non-life threat. pronounced symptoms	2
	D-D [Minimal symptoms (skin, eye or resp)	6
	TOTAL	8

Species: Human

		Route of Admin
		Other
EPA Classification	H-D [Minimal symptoms (skin, eye, or resp)	2
	TOTAL	2

Summary for ALL Species

		Route of Admin
		Other
EPA Classification	D-A [Death]	1
	D-B [Life threatening &/or residual disability]	3
	D-C [Non-life threat. pronounced symptoms, no disability]	8
	D-D [Minimal symptoms (skin, eye or resp) resolved rapidly]	32

		Route of Admin
		Other
EPA Classification	D-E [Symptoms unknown or not specified]	0
	G-A [Water Contamination - see guidelines]	0
	G-B [Water Contamination - see guidelines]	0
	G-C [Water Contamination - see guidelines]	0
	H-A [Person Died]	0
	H-B [Life threat. ,repro effects, &/or residual disability]	0
	H-C [Non-life threat. pronounced symptoms, no disability]	0
	H-D [Minimal symptoms (skin, eye, or resp) resolved rapidly]	2
	H-E [Symptoms unknown, unspecified or "delayed or chronic"]	0
	ONT [Other Non-Target Organisms]	0
	P-A [Plant - >45% of acreage exposed]	0
	P-B [Plant - <45% of acreage exposed]	0
	PD-A [Alleged damage that could have caused human injury]	0
	PD-B [Alleged to have caused damage >$5,000]	0
	PD-C [other allegations not in PD-A or B]	0
	W-A [Fish or Wildlife - see EPA guidelines]	0
	W-B [Fish or Wildlife - see EPA guidelines]	0
	TOTAL	**46**

NB: Counts reflect the numbers of doses for cases with EPA products - these may differ from the number of distinct case reports. (Data columns which return no values are suppressed).

Secondary Exposure Incident Count

*** No records found ***

NB: Counts reflect the number of products having secondary exposure - these may differ from the number of distinct case reports

Incident Count by Severity Code and Age

		EPA Classification					
		D-A	D-B	D-C	D-D	H-D	Unassessed
Age Category	<3 months	0	0	0	1	0	0
	3-6 months	0	0	0	2	0	0
	6-9 months	0	0	0	0	0	0
	9-12 months	0	0	0	1	0	0
	1 year	0	0	1	2	0	0
	2 years	0	1	1	2	0	0
	3 years	0	0	0	1	0	0
	4 years	0	1	2	2	0	0
	5 years	0	0	2	2	0	0
	6 years	0	0	0	2	0	0
	7 years	0	0	0	2	0	0
	8 years	0	0	0	1	0	0
	9 years	0	0	0	3	0	0
	10 years	0	0	0	2	0	0
	11 years	0	0	0	2	0	0
	12 years	0	0	0	1	0	0
	13 years	0	0	0	2	0	0
	14 years	0	1	0	2	0	0
	15 years	0	0	0	0	0	0
	> 15 years	1	0	0	0	2	0
	not specified	0	0	2	2	0	0
	TOTAL	1	3	8	32	2	0

NB: Counts reflect the number of patients for cases with EPA products - these may differ from the number of distinct case reports. (Data columns which return no values are suppressed).

Incident Count by Severity Code and Weight

		EPA Classification				
		D-A	D-B	D-C	D-D	H-D
Weight Category	< 21lbs	*0*	*0*	*2*	*7*	*0*
	21 - 38lbs	*0*	*0*	*3*	*15*	*0*
	38 - 55lbs	*1*	*2*	*3*	*6*	*0*
	> 55lbs	*0*	*1*	*0*	*2*	*0*
	not specifled	*0*	*0*	*0*	*2*	*2*
	TOTAL	**1**	**3**	**8**	**32**	**2**

NB: Counts reflect the number of patients for cases with EPA products - these may differ from the number of distinct case reports. (Data columns which return no values are suppressed).

Incident Count by Breed

Species: Canine		Incident count	
Breed	Mixed Breed (Canine)	8	22
	Pit Bull	5	13
	Beagle	3	8
	Bichon Frise	2	5
	Retriever (Labrador, Black)	2	5
	Retriever (N. Scotia Duck Tolling)	2	5
	Unknown Breed (Canine)	2	5
	Basset Hound	1	2
	Border Collie	1	2
	Bouvier Des Flandres	1	2
	Bulldog	1	2
	Cockapoo	1	2
	French Bulldog	1	2
	Pekingese	1	2
	Poodle (Toy)	1	2
	Schnauzer	1	2
	Siberian Husky	1	2
	Spaniel (Cocker)	1	2
	Terrier (Jack Russell)	1	2
	TOTAL	36	100

Species: Feline		Incident count	
Breed	Domestic Shorthair	7	87
	Siamese	1	12
	TOTAL	8	100

Species: Human		Incident count	
Breed	Unknown	2	100
	TOTAL	2	100

Summary for ALL Species

		Incident count	
Species	Canine	*36*	78%
	Feline	*8*	17%
	Human	*2*	4%
	TOTAL	*46*	100%

NB: Counts reflect the number of patients for cases with EPA products - these may differ from the number of distinct case reports

Incident Count by Clinical Sign - Summary

System Organ Class	Incident Count	
Skin and appendages disorders	*25*	26 %
Systemic disorders	*15*	15 %
Digestive tract disorders	*14*	14 %
Behavioural disorders	*11*	11 %
Application site disorders	*8*	8 %
Neurological disorders	*6*	6 %
Eye disorders	*5*	5 %
Renal and urinary disorders	*3*	3 %
Respiratory tract disorders	*3*	3 %
Unknown	*3*	3 %
Immune system disorders	*2*	2 %
Hepato-biliary disorders	*1*	
Musculoskeletal disorders	*1*	
GRAND TOTAL:	*97*	

NB: Counts reflect number of signs for cases with EPA products - these may differ from the number of distinct case reports

Validation Report

EPA Summary Report

Cases first valid from: 01-Jan-2013 to: 31-Mar-2013

Parameters:
For Brand : Advantage II Small Dog

Incident Count by Severity Code and Route of Exposure

Species: Canine

		Route of Admin
		Other
EPA Classification	D-A [Death]	3
	D-C [Non-life threat. pronounced symptoms	4
	D-D [Minimal symptoms (skin, eye or resp)	26
	TOTAL	33

Species: Feline

		Route of Admin
		Other
EPA Classification	D-C [Non-life threat. pronounced symptoms	1
	TOTAL	1

Summary for ALL Species

		Route of Admin
		Other
EPA Classification	D-A [Death]	3
	D-B [Life threatening &/or residual disability]	0
	D-C [Non-life threat. pronounced symptoms, no disability]	5
	D-D [Minimal symptoms (skin, eye or resp) resolved rapidly]	26
	D-E [Symptoms unknown or not specified]	0
	G-A [Water Contamination - see guidelines]	0
	G-B [Water Contamination - see guidelines]	0
	G-C [Water Contamination - see guidelines]	0
	H-A [Person Died]	0

		Route of Admin
		Other
EPA Classification	H-B [Life threat. ,repro effects, &/or residual disability]	0
	H-C [Non-life threat. pronounced symptoms, no disability]	0
	H-D [Minimal symptoms (skin, eye, or resp) resolved rapidly]	0
	H-E [Symptoms unknown, unspecified or "delayed or chronic"]	0
	ONT [Other Non-Target Organisms]	0
	P-A [Plant - >45% of acreage exposed]	0
	P-B [Plant - <45% of acreage exposed]	0
	PD-A [Alleged damage that could have caused human injury]	0
	PD-B [Alleged to have caused damage >$5,000]	0
	PD-C [other allegations not in PD-A or B]	0
	W-A [Fish or Wildlife - see EPA guidelines]	0
	W-B [Fish or Wildlife - see EPA guidelines]	0
	TOTAL	34

NB: Counts reflect the numbers of doses for cases with EPA products - these may differ from the number of distinct case reports. (Data columns which return no values are suppressed).

Secondary Exposure Incident Count

*** No records found ***

NB: Counts reflect the number of products having secondary exposure - these may differ from the number of distinct case reports

Incident Count by Severity Code and Age

Age Category	EPA Classification			
	D-A	D-C	D-D	Unassessed
<3 months	0	0	0	0
3-6 months	0	0	2	0
6-9 months	0	2	0	0
9-12 months	0	0	1	0
1 year	0	0	3	0
2 years	0	0	4	0
3 years	0	0	3	0
4 years	0	0	1	0
5 years	0	0	2	0
6 years	0	0	0	0
7 years	0	1	2	0
8 years	1	0	0	0
9 years	0	0	2	0
10 years	0	0	1	0
11 years	0	1	2	0
12 years	1	0	0	0
13 years	0	0	0	0
14 years	0	0	1	0
15 years	0	0	0	0
> 15 years	1	0	0	0
not specified	0	1	2	0
TOTAL	3	5	26	0

NB: Counts reflect the number of patients for cases with EPA products - these may differ from the number of distinct case reports. (Data columns which return no values are suppressed).

Incident Count by Severity Code and Weight

		EPA Classification			
		D-A	D-C	D-D	Unassessed
Weight Category	< 1lbs	*0*	*0*	*0*	*0*
	1 - 5lbs	*0*	*0*	*2*	*0*
	5 - 10lbs	*1*	*2*	*17*	*0*
	> 10lbs	*1*	*2*	*6*	*0*
	not specified	*1*	*1*	*1*	*0*
	TOTAL	3	5	26	0

NB: Counts reflect the number of patients for cases with EPA products - these may differ from the number of distinct case reports. (Data columns which return no values are suppressed).

Incident Count by Breed

Species: Canine		Incident count
Breed	Chihuahua	10
	Maltese	4
	Mixed Breed (Canine)	4
	Pomeranian	4
	Schnauzer	2
	Shih Tzu	2
	Yorkshire Terrier	2
	Dachshund	1
	Pinscher (Miniature)	1
	Terrier (Rat)	1
	Unknown Breed (Canine)	1
	West Highland White	1
	TOTAL	33

Species: Feline		Incident count
Breed	Domestic Longhair	1
	TOTAL	1

Summary for ALL Species

		Incident count
Species	Canine	33
	Feline	1
	TOTAL	34

NB: Counts reflect the number of patients for cases with EPA products - these may differ from the number of distinct case reports

Incident Count by Clinical Sign - Summary

System Organ Class	Incident Count	
Skin and appendages disorders	32	48%
Systemic disorders	12	18%
Behavioural disorders	6	9%
Digestive tract disorders	6	9%
Eye disorders	3	4%
Respiratory tract disorders	3	4%
Cardio-vascular system disorders	2	3%
Application site disorders	1	1%
Endocrine system disorders	1	1%
Neurological disorders	1	1%
GRAND TOTAL:	67	

NB: Counts reflect number of signs for cases with EPA products - these may differ from the number of distinct case reports

Validation Report

EPA Summary Report

Cases first valid from: 01-Jan-2013 to: 31-Mar-2013

Parameters:
For Brand : Advantage II Extra Large Dog

Incident Count by Severity Code and Route of Exposure

Species: Canine

		Route of Admin
		Other
EPA Classification	D-A [Death]	2
	D-B [Life threatening &/or residual disabilit	4
	D-C [Non-life threat. pronounced symptoms	12
	D-D [Minimal symptoms (skin, eye or resp)	21
	TOTAL	**39**

Species: Feline

		Route of Admin	
		Oral	Other
EPA Classification	D-C [Non-life threat. pronounced symptoms	0	1
	D-D [Minimal symptoms (skin, eye or resp)	1	2
	TOTAL	**1**	**3**

Species: Human

		Route of Admin
		Other
EPA Classification	H-D [Minimal symptoms (skin, eye, or resp)	1
	TOTAL	**1**

Summary for ALL Species

		Route of Admin	
		Oral	Other
EPA Classification	D-A [Death]	0	2
	D-B [Life threatening &/or residual disabilit]	0	4
	D-C [Non-life threat. pronounced symptoms, no disabilit]	0	13
	D-D [Minimal symptoms (skin, eye or resp) resolved rapidly]	1	23

		Route of Adm...	
		Oral	Other
EPA Classification	D-E [Symptoms unknown or not specified]	0	0
	G-A [Water Contamination - see guidelines]	0	0
	G-B [Water Contamination - see guidelines]	0	0
	G-C [Water Contamination - see guidelines]	0	0
	H-A [Person Died]	0	0
	H-B [Life threat. ,repro effects, &/or residual disability]	0	0
	H-C [Non-life threat. pronounced symptoms, no disability]	0	0
	H-D [Minimal symptoms (skin, eye, or resp) resolved rapidly]	0	1
	H-E [Symptoms unknown, unspecified or "delayed or chronic"]	0	0
	ONT [Other Non-Target Organisms]	0	0
	P-A [Plant - >45% of acreage exposed]	0	0
	P-B [Plant - <45% of acreage exposed]	0	0
	PD-A [Alleged damage that could have caused human injury]	0	0
	PD-B [Alleged to have caused damage >$5,000]	0	0
	PD-C [other allegations not in PD-A or B]	0	0
	W-A [Fish or Wildlife - see EPA guidelines]	0	0
	W-B [Fish or Wildlife - see EPA guidelines]	0	0
	TOTAL	**1**	**43**

NB: Counts reflect the numbers of doses for cases with EPA products - these may differ from the number of distincl case reports.
(Data columns which return no values are suppressed).

Secondary Exposure Incident Count

*** No records found ***

NB: Counts reflect the number of products having secondary exposure - these may differ from the number of distinct case reports

Incident Count by Severity Code and Age

Age Category	EPA Classification					
	D-A	D-B	D-C	D-D	H-D	Unassessed
<3 months	0	0	0	0	0	0
3-6 months	0	0	0	0	0	0
6-9 months	0	0	0	2	0	0
9-12 months	0	0	0	0	0	0
1 year	0	0	0	1	0	0
2 years	0	0	1	2	0	0
3 years	0	1	1	2	0	0
4 years	0	0	0	2	0	0
5 years	0	0	3	1	0	0
6 years	0	0	1	3	0	0
7 years	0	1	0	1	0	0
8 years	0	1	1	1	0	0
9 years	0	0	0	4	0	0
10 years	0	0	1	2	0	0
11 years	0	1	0	2	0	0
12 years	0	0	2	0	0	0
13 years	0	0	0	0	0	0
14 years	1	0	2	0	0	0
15 years	0	0	0	1	0	0
> 15 years	0	0	0	0	1	0
not specified	1	0	1	0	0	0
TOTAL	2	4	13	24	1	0

NB: Counts reflect the number of patients for cases with EPA products - these may differ from the number of distinct case reports.
(Data columns which return no values are suppressed).

Incident Count by Severity Code and Weight

		EPA Classification				
		D-A	D-B	D-C	D-D	H-D
Weight Category	< 56lbs	0	0	3	7	0
	56 - 78lbs	0	3	6	12	0
	78 - 100lbs	0	1	2	1	0
	> 100lbs	0	0	1	3	0
	not specified	2	0	1	1	1
	TOTAL	2	4	13	24	1

NB: Counts reflect the number of patients for cases with EPA products - these may differ from the number of distinct case reports.
(Data columns which return no values are suppressed).

Incident Count by Breed

Species: Canine		Incident count
Breed	Mixed Breed (Canine)	9
	Retriever (Golden)	4
	Retriever Labrador (No Description)	3
	Dachshund	2
	Old English Sheep Dog	2
	Pit Bull	2
	Rhodesian Ridgeback	2
	Unknown Breed (Canine)	2
	American Eskimo	1
	Bloodhound	1
	Boxer	1
	Doberman Pinscher	1
	German Shepherd Dog	1
	Great Dane	1
	Greyhound	1
	Mastiff	1
	Pinscher (Miniature)	1
	Pointer (German Short-Haired)	1
	Poodle (Standard)	1
	Rottweiler	1
	Siberian Husky	1
	TOTAL	39

Species: Feline		Incident count
Breed	Domestic Longhair	2
	Domestic Shorthair	1
	Manx	1
	TOTAL	4

Species: Human		Incident count	
Breed	Unknown	1	100%
	TOTAL	1	100%

Summary for ALL Species

		Incident count	
Species	Canine	39	88%
	Feline	4	9%
	Human	1	2%
	TOTAL	44	100%

NB: Counts reflect the number of patients for cases with EPA products - these may differ from the number of distinct case reports

Incident Count by Clinical Sign - Summary

System Organ Class	Incident Count	
Skin and appendages disorders	31	32%
Systemic disorders	20	20%
Behavioural disorders	12	12%
Neurological disorders	8	8%
Digestive tract disorders	7	7%
Application site disorders	5	5%
Musculoskeletal disorders	3	3%
Unknown	3	3%
Hepato-biliary disorders	2	2%
Immune system disorders	2	2%
Respiratory tract disorders	2	2%
Blood and lymphatic system disorders	1	1%
Ear and labyrinth disorders	1	1%
Eye disorders	1	1%
GRAND TOTAL:	98	

NB: Counts reflect number of signs for cases with EPA products - these may differ from the number of distinct case reports

Validation Report

EPA Summary Report

Cases first valid from: 01-Jan-2013 to: 31-Mar-2013

Parameters:
For Brand : Advantage II Kitten

Incident Count by Severity Code and Route of Exposure

Species: Feline

		Route of Admin
		Other
EPA Classification	D-B [Life threatening &/or residual disabilit	1
	D-C [Non-life threat. pronounced symptoms	1
	D-D [Minimal symptoms (skin, eye or resp)	10
	TOTAL	**12**

Species: Rabbit

		Route of Admin
		Other
EPA Classification	D-D [Minimal symptoms (skin, eye or resp)	1
	TOTAL	**1**

Summary for ALL Species

		Route of Admin
		Other
EPA Classification	D-A [Death]	0
	D-B [Life threatening &/or residual disability]	1
	D-C [Non-life threat. pronounced symptoms, no disability]	1
	D-D [Minimal symptoms (skin, eye or resp) resolved rapidly]	11
	D-E [Symptoms unknown or not specified]	0
	G-A [Water Contamination - see guidelines]	0
	G-B [Water Contamination - see guidelines]	0
	G-C [Water Contamination - see guidelines]	0
	H-A [Person Died]	0

		Route of Admin
		Other
EPA Classification	H-B [Life threat. ,repro effects, &/or residual disability]	0
	H-C [Non-life threat. pronounced symptoms, no disability]	0
	H-D [Minimal symptoms (skin, eye, or resp) resolved rapidly]	0
	H-E [Symptoms unknown, unspecified or "delayed or chronic"]	0
	ONT [Other Non-Target Organisms]	0
	P-A [Plant - >45% of acreage exposed]	0
	P-B [Plant - <45% of acreage exposed]	0
	PD-A [Alleged damage that could have caused human injury]	0
	PD-B [Alleged to have caused damage >$5,000]	0
	PD-C [other allegations not in PD-A or B]	0
	W-A [Fish or Wildlife - see EPA guidelines]	0
	W-B [Fish or Wildlife - see EPA guidelines]	0
	TOTAL	13

NB: Counts reflect the numbers of doses for cases with EPA products - these may differ from the number of distinct case reports. (Data columns which return no values are suppressed).

Secondary Exposure Incident Count

*** No records found ***

NB: Counts reflect the number of products having secondary exposure - these may differ from the number of distinct case reports

Incident Count by Severity Code and Age

		EPA Classification			
		D-B	D-C	D-D	Unassessed
Age Category	<3 months	0	0	2	0
	3-6 months	0	1	6	0
	6-9 months	0	0	1	0
	9-12 months	0	0	0	0
	1 year	0	0	0	0
	2 years	0	0	0	0
	3 years	0	0	0	0
	4 years	0	0	0	0
	5 years	0	0	0	0
	6 years	0	0	1	0
	7 years	0	0	0	0
	8 years	1	0	0	0
	9 years	0	0	0	0
	10 years	0	0	0	0
	11 years	0	0	0	0
	12 years	0	0	0	0
	13 years	0	0	1	0
	14 years	0	0	0	0
	15 years	0	0	0	0
	> 15 years	0	0	0	0
	not specified	0	0	0	0
	TOTAL	1	1	11	0

NB: Counts reflect the number of patients for cases with EPA products - these may differ from the number of distinct case reports.
(Data columns which return no values are suppressed).

Incident Count by Severity Code and Weight

		EPA Classification			
		D-B	D-C	D-D	Unassessed
Weight Category	< 1lbs	*0*	*0*	*0*	*0*
	1 - 2lbs	*0*	*0*	*0*	*0*
	2 - 4lbs	*0*	*0*	*4*	*0*
	> 4lbs	*1*	*1*	*3*	*0*
	not specified	*0*	*0*	*4*	*0*
	TOTAL	1	1	11	0

NB: Counts reflect the number of patients for cases with EPA products - these may differ from the number of distinct case reports.
(Data columns which return no values are suppressed).

Incident Count by Breed

Species: Feline		Incident count	
Breed	Domestic Shorthair	9	75%
	Domestic Longhair	1	8%
	Mixed Breed (Feline)	1	8%
	Tonkinese	1	8%
	TOTAL	12	100%

Species: Rabbit		Incident count	
Breed	Unknown Breed (Rabbit)	1	100%
	TOTAL	1	100%

Summary for ALL Species

		Incident count	
Species	Feline	12	92%
	Rabbit	1	8%
	TOTAL	13	100%

NB: Counts reflect the number of patients for cases with EPA products - these may differ from the number of distinct case reports

Incident Count by Clinical Sign - Summary

System Organ Class	Incident Count	
Digestive tract disorders	6	35%
Skin and appendages disorders	5	29%
Behavioural disorders	3	18%
Systemic disorders	2	12%
Application site disorders	1	6%
GRAND TOTAL:	17	

NB: Counts reflect number of signs for cases with EPA products - these may differ from the number of distinct case reports

Validation Report

EPA Summary Report

Cases first valid from: 01-Jan-2013 to: 31-Mar-2013

Parameters:
For Brand : Advantage II Small Cat

Incident Count by Severity Code and Route of Exposure

Species: Feline

		Route of Admin
		Other
EPA Classification	D-A [Death]	2
	D-B [Life threatening &/or residual disabilit	4
	D-C [Non-life threat. pronounced symptoms	15
	D-D [Minimal symptoms (skin, eye or resp)	40
	TOTAL	61

Species: Human

		Route of Admin
		Other
EPA Classification	H-C [Non-life threat. pronounced symptoms	1
	H-D [Minimal symptoms (skin, eye, or resp)	1
	TOTAL	2

Summary for ALL Species

		Route of Admin
		Other
EPA Classification	D-A [Death]	2
	D-B [Life threatening &/or residual disabilityl	4
	D-C [Non-life threat. pronounced symptoms, no disabilityl	15
	D-D [Minimal symptoms (skin, eye or resp) resolved rapidlyl	40
	D-E [Symptoms unknown or not specified]	0
	G-A [Water Contamination - see guidelines]	0
	G-B [Water Contamination - see guidelines]	0
	G-C [Water Contamination - see guidelines]	0
	H-A [Person Died]	0

		Route of Admin
		Other
EPA Classification	H-B [Life threat. ,repro effects, &/or residual disability]	*0*
	H-C [Non-life threat. pronounced symptoms, no disability]	*1*
	H-D [Minimal symptoms (skin, eye, or resp) resolved rapidly]	*1*
	H-E [Symptoms unknown, unspecified or "delayed or chronic"]	*0*
	ONT [Other Non-Target Organisms]	*0*
	P-A [Plant - >45% of acreage exposed]	*0*
	P-B [Plant - <45% of acreage exposed]	*0*
	PD-A [Alleged damage that could have caused human injury]	*0*
	PD-B [Alleged to have caused damage >$5,000]	*0*
	PD-C [other allegations not in PD-A or B]	*0*
	W-A [Fish or Wildlife - see EPA guidelines]	*0*
	W-B [Fish or Wildlife - see EPA guidelines]	*0*
	TOTAL	**63**

NB: Counts reflect the numbers of doses for cases with EPA products - these may differ from the number of distinct case reports. (Data columns which return no values are suppressed).

Secondary Exposure Incident Count

Species: Feline	Incident Count
Feline	1
TOTAL	1

Species: Human	Incident Count
Human	2
TOTAL	2

Summary for all Species

	Incident Count
Human	2
Feline	1
TOTAL	3

NB: Counts reflect the number of products having secondary exposure - these may differ from the number of distinct case reports

Incident Count by Severity Code and Age

Age Category	EPA Classification						
	D-A	D-B	D-C	D-D	H-C	H-D	Unassessed
<3 months	0	0	0	0	0	0	0
3-6 months	0	0	1	1	0	0	0
6-9 months	0	1	0	6	0	0	0
9-12 months	0	0	0	4	0	0	0
1 year	0	1	3	1	0	0	0
2 years	0	1	2	2	0	0	0
3 years	0	0	0	3	0	0	0
4 years	0	0	2	4	0	0	0
5 years	0	0	3	3	1	0	0
6 years	0	0	0	1	0	0	0
7 years	0	0	0	3	0	0	0
8 years	0	0	1	1	0	0	0
9 years	0	0	0	0	0	0	0
10 years	1	0	0	1	0	0	0
11 years	0	0	0	0	0	0	0
12 years	0	0	0	0	0	0	0
13 years	0	0	1	2	0	0	0
14 years	1	0	0	0	0	0	0
15 years	0	1	0	4	0	0	0
> 15 years	0	0	1	1	0	1	0
not specified	0	0	1	3	0	0	0
TOTAL	2	4	15	40	1	1	0

NB: Counts reflect the number of patients for cases with EPA products - these may differ from the number of distinct case reports.
(Data columns which return no values are suppressed).

Incid[illegible] Count by Severity Code and We[illegible]t

		EPA Classification					
		D-A	D-B	D-C	D-D	H-C	H-D
Weight Category	< 5lbs	0	0	1	0	0	0
	5 - 7lbs	0	1	5	11	0	0
	7 - 9lbs	0	2	1	9	0	0
	> 9lbs	0	0	7	16	0	0
	not specified	2	1	1	4	1	1
	TOTAL	2	4	15	40	1	1

NB: Counts reflect the number of patients for cases with EPA products - these may differ from the number of distinct case reports. (Data columns which return no values are suppressed).

Incident Count by Breed

Species: Feline		Incident count
Breed	Domestic Shorthair	34
	Domestic Longhair	8
	Siamese	5
	Unknown Breed (Feline)	4
	Domestic Mediumhair	3
	Abyssinian	2
	Persian	2
	American Shorthair	1
	Mixed Breed (Feline)	1
	Ragdoll	1
	TOTAL	61

Species: Human		Incident count
Breed	Unknown	2
	TOTAL	2

Summary for ALL Species

		Incident count
Species	Feline	61
	Human	2
	TOTAL	63

NB: Counts reflect the number of patients for cases with EPA products - these may differ from the number of distinct case reports

Incident Count by Clinical Sign - Summary

System Organ Class	Incident Count	
Skin and appendages disorders	37	28%
Systemic disorders	27	20%
Behavioural disorders	18	14%
Digestive tract disorders	18	14%
Neurological disorders	12	9%
Application site disorders	8	6%
Unknown	5	4%
Blood and lymphatic system disorders	3	2%
Respiratory tract disorders	2	2%
Ear and labyrinth disorders	1	
Eye disorders	1	
Immune system disorders	1	
GRAND TOTAL:	133	

NB: Counts reflect number of signs for cases with EPA products - these may differ from the number of distinct case reports

Validation Report

EPA Summary Report

Cases first valid from: 01-Jan-2013 to: 31-Mar-2013

Parameters:
For Brand : Advantage II Large Cat

Incident Count by Severity Code and Route of Exposure

Species: Feline

		Route of Admin
		Other
EPA Classification	D-A [Death]	7
	D-B [Life threatening &/or residual disabilit	12
	D-C [Non-life threat. pronounced symptoms	37
	D-D [Minimal symptoms (skin, eye or resp)	140
	TOTAL	**196**

Species: Human

		Route of Admin
		Other
EPA Classification	H-C [Non-life threat. pronounced symptoms	3
	H-D [Minimal symptoms (skin, eye, or resp)	3
	TOTAL	**6**

Summary for ALL Species

		Route of Admin
		Other
EPA Classification	D-A [Death]	7
	D-B [Life threatening &/or residual disabilityl	12
	D-C [Non-life threat. pronounced symptoms, no disabilityl	37
	D-D [Minimal symptoms (skin, eye or resp) resolved rapidlyl	140
	D-E [Symptoms unknown or not specified]	0
	G-A [Water Contamination - see guidelines]	0
	G-B [Water Contamination - see guidelines]	0
	G-C [Water Contamination - see guidelines]	0
	H-A [Person Died]	0

		Route of Admin
		Other
EPA Classification	H-B [Life threat. ,repro effects, &/or residual disability]	*0*
	H-C [Non-life threat. pronounced symptoms, no disability]	*3*
	H-D [Minimal symptoms (skin, eye, or resp) resolved rapidly]	*3*
	H-E [Symptoms unknown, unspecified or "delayed or chronic"]	*0*
	ONT [Other Non-Target Organisms]	*0*
	P-A [Plant - >45% of acreage exposed]	*0*
	P-B [Plant - <45% of acreage exposed]	*0*
	PD-A [Alleged damage that could have caused human injury]	*0*
	PD-B [Alleged to have caused damage >$5,000]	*0*
	PD-C [other allegations not in PD-A or B]	*0*
	W-A [Fish or Wildlife - see EPA guidelines]	*0*
	W-B [Fish or Wildlife - see EPA guidelines]	*0*
	TOTAL	**202**

NB: Counts reflect the numbers of doses for cases with EPA products - these may differ from the number of distinct case reports.
(Data columns which return no values are suppressed).

Secondary Exposure Incident Count

Species: Human	Incident Count
Human	3
TOTAL	3

Summary for all Species

	Incident Count
Human	3
TOTAL	3

NB: Counts reflect the number of products having secondary exposure - these may differ from the number of distinct case reports

Incident Count by Severity Code and Age

Age Category	EPA Classification						
	D-A	D-B	D-C	D-D	H-C	H-D	Unassessed
<3 months	0	0	0	0	0	0	0
3-6 months	0	1	0	2	0	0	0
6-9 months	0	0	1	2	0	0	0
9-12 months	0	0	0	8	0	0	0
1 year	0	2	3	16	0	0	0
2 years	2	0	5	14	0	0	0
3 years	0	0	1	8	0	0	0
4 years	0	0	2	10	0	0	0
5 years	0	0	3	10	0	0	0
6 years	0	1	3	11	0	0	0
7 years	1	1	4	7	0	0	0
8 years	0	2	0	5	0	0	0
9 years	0	1	4	7	0	0	0
10 years	0	0	0	10	0	0	0
11 years	1	1	3	6	0	0	0
12 years	0	2	1	4	0	0	0
13 years	0	0	2	6	0	0	0
14 years	0	1	2	2	0	0	0
15 years	1	0	2	0	0	0	0
> t5 years	1	0	1	4	2	1	0
not specified	1	0	0	8	1	2	0
TOTAL	7	12	37	140	3	3	0

NB: Counts reflect the number of patients for cases with EPA products - these may differ from the number of distinct case reports. (Data columns which return no values are suppressed).

Incid[illegible] Count by Severity Code and W[illegible]t

		EPA Classification					
		D-A	D-B	D-C	D-D	H-C	H-D
Weight Category	< 9lbs	2	0	2	12	0	0
	9 - 14lbs	1	3	23	83	0	0
	14 - 20lbs	2	8	7	24	0	0
	> 20lbs	0	0	2	13	1	0
	not specified	2	1	3	8	2	3
	TOTAL	7	12	37	140	3	3

NB: Counts reflect the number of patients for cases with EPA products - these may differ from the number of distinct case reports. (Data columns which return no values are suppressed).

Incident Count by Breed

Species: Feline		Incident count
Breed	Domestic Shorthair	112
	Domestic Longhair	35
	Unknown Breed (Feline)	11
	Domestic Mediumhair	9
	Persian	5
	Maine Coon Cat	4
	American Shorthair	3
	Burmese	3
	Russian Blue	3
	Bengal	2
	Manx	2
	Ragdoll	2
	Siamese	2
	Calico	1
	Devon Rex	1
	Tonkinese	1
	TOTAL	196

Species: Human		Incident count
Breed	Unknown	6
	TOTAL	6

Summary for ALL Species

		Incident count
Species	Feline	196
	Human	6
	TOTAL	202

NB: Counts reflect the number of patients for cases with EPA products - these may differ from the number of distinct case reports

Incident Count by Clinical Sign - Summary

System Organ Class	Incident Count	
Application site disorders	***74***	19%
Skin and appendages disorders	***67***	17%
Systemic disorders	***67***	17%
Behavioural disorders	***58***	15%
Digestive tract disorders	***56***	15%
Neurological disorders	***28***	7%
Renal and urinary disorders	***9***	2%
Eye disorders	***8***	2%
Respiratory tract disorders	***8***	2%
Ear and labyrinth disorders	***6***	2%
Unknown	***4***	1%
Endocrine system disorders	***1***	0%
GRAND TOTAL:	***386***	

NB: Counts reflect number of signs for cases with EPA products - these may differ from the number of distinct case reports

Validation Report

Bayer HealthCare
Animal Health

November 28, 2012

Document Processing Desk
Office of Pesticide Programs (7504P) – NonPRIA
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Attention: Ms. Venus Eagle/PM01

Subject: Advantage II Kitten (EPA Reg. No. 11556-150)
Advantage II Small Cat (EPA Reg. No. 11556-151)
Advantage II Large Cat (EPA Reg. No. 11556-152)
Advantage II Small Dog (EPA Reg. No. 11556-128)
Advantage II Medium Dog (EPA Reg. No. 11556-125)
Advantage II Large Dog (EPA Reg. No. 11556-127)
Advantage II Extra Large Dog (EPA Reg. No. 11556-130)

Bayer HealthCare LLC
Animal Health
P.O. Box 390
Shawnee Mission, KS 66201-0390

Please find enclosed the conditional registration requirement of enhanced quarterly incident report for Advantage II Dog and Cat registrations for the quarter starting July 1, 2012.

This submission includes the following tables covering incident reporting from July 1, 2012 through September 30, 2012:

Summary Table (multiple pages due to length)
Breed Summary
Age Range Summary
Clinical Signs Summary
Organ System Summary
Patient Weight Range Summary
Product Weight Range Summary
Route of Exposure Summary
Secondary Exposure Summary

Due to the length of some of the tables and to provide the Agency the ability to sort, this data is being provided electronically on a CD. The data was extracted from Bayer's pharmacovigilance data base (P.V. Works).

Deaths:
Advantage II for Cats Deaths for Reports with a Date First Valid between 01 Jul 2012 and 30 Sep 2012 Inclusive

*Included in the Summaries are reports not factored into statistical analysis as the products were for Advantage II (unspecified).

2012-US0028623
Summary:
Due to the sensitive nature of the situation, specifics of this event are unknown, therefore this was reported as such. On approximately 20-Jun-2012, an unknown old, Unknown Breed feline, in unknown condition, was administered 1 tube of Advantage II Small Cat (Imidacloprid-Pyriproxyfen) once topically by the owner. The cat has no known concomitant medical conditions. On approximately 01-Jul-2012 the cat died due to an unknown cause.

Assessment:
Death is never expected following the application of Advantage II. The product is safe and non-toxic and the cause of death is unknown. The owner called to ask questions regarding flea treatment for her cats and dogs and mentioned the one of her cats died recently.

2012-US0029001
Summary:
On approximately 01-May-2012, a 7 pound, female, Unknown Breed feline, in poor condition, was administered 1 tube of Advantage II Large Cat (Imidacloprid-Pyriproxyfen) once topically by the owner. The cat had a kidney mass. On 29-May-2012 the cat died. After death there was a palpable mass on the cat's kidneys.

Assessment:
Death is never expected following the application of a topical product. Without further information, it is unknown what, if any, role the product could have had in this event. The cat's owner called for information on another product and mentioned during the phone call that this cat had passed away.

2012-US0029321
Summary:
On 11Jul2012, a 2 year old, 8 pound, spayed, female, Domestic Shorthair feline, in good condition, with no known concomitant medical conditions, was administered 1 tube of Advantage II Small Cat (Imidacloprid-Pyriproxyfen) once topically by the owner. 12Jul2012 the patient was found deceased. No necropsy was able to be performed as the patient's remains had already been disposed of.

Assessment:
Death would not be expected with proper use of this topically active product. No necropsy was able to be performed. Therefore the cause of death cannot be determined.

What role, if any, the product played in this case can also not be determined. No quality issues were noted upon product investigation.

2012-US0030966

Summary:

On approximately 20-Jul-2012, a 2 year old, 5.70 pound, male, Domestic Shorthair feline, in good condition, with no known concomitant medical conditions, was administered 1 tube of Advantage II Small Cat (Imidacloprid-Pyriproxyfen) once topically by the owner. Approximately 1.5 hours post application, the cat was ataxic (could not walk and unable to stand because he is falling over), had mydriasis, was vocalizing, and was laying in an abnormal area in the home (behavioral). On 22-Jul-2012 the cat passed away. The case is being reported with minimal information. Unsuccessful contact attempts have been made to obtain more information.

Assessment:

The clinical signs exhibited prior to the death of the patient are not indicative of intoxication with either of the active ingredients. The cause of death is unknown despite attempts to obtain further information. What role, if any, the product played in this case cannot be determined.

2012-US0030977

Summary:

On 20Jul2012, an 8 year old, 11.00 pound, male, Domestic Shorthair feline, in good condition, with no known concomitant medical conditions, was administered 1 tube of Advantage II Large Cat (Imidacloprid-Pyriproxyfen) once topically by the owner. At the same time, a dog in the house also had K9 Advantix II Extra Large Dog applied. On 21Jul2012 (Approximately 7.5 hours post application) the patient developed ataxia and began panting. The patient was evaluated by a veterinarian and unknown treatments were performed. The patient's signs progressed into seizures and it was decided to euthanize the patient on an unspecified date.

Assessment:

Clinical signs and outcome of this nature are not known to occur to imidacloprid or pyriproxyfen. A specific diagnosis for the clinical signs exhibited could not be provided.

2012-US0033328

Summary:

On 14-May-2012, a 12 year old, 12 pound, neutered, male, Domestic Shorthair feline, in fair condition, with diabetes mellitus and rash, was administered 1 tube of Advantage II Large Cat (Imidacloprid-Pyriproxyfen) once topically by the owner. The diabetes is controlled with twice daily insulin. The cat was fine after application of the product and had used the product the prior 2 months with no issues. Owner stated that the tubes seemed to have more liquid in them. On 28-May-2012 two weeks post application of the product, the cat passed away. No necropsy was performed.

Assessment:
No necropsy was performed and the body has already been taken care of. Without a necropsy, it is impossible to determine what other disease process played a part in the animal's death. No quality issues were noted upon product investigation.

2012-US0034319

Summary:
On an unknown date, a 15 year old, feline, whose age, weight, and condition are unknown, was administered 1 tube of Advantage II Small Cat (Imidacloprid-Pyriproxyfen) once topically by the owner. At an undetermined time after application the patient developed a thyroid condition and was subsequently euthanized on an unknown date. Due to the nature of the communication, more specific information could not be obtained; the case will be reported with the limited information available.

Assessment:
Thyroid disease would not be expected after proper use of this topically active product. The patient was elderly and thyroid disease is no uncommon in elderly cats. Product involvement is unlikely. The patient was then subsequently euthanized due to its condition. No quality issues were noted upon product investigation.

2012-US0035252

Summary:
On 22-Jul-2012, a 4 year old, 10 pound, spayed, female, Domestic Shorthair feline, in fair condition, with an active flea infestation and a lower urinary tract disease, was administered 1 tube of Advantage II Large Cat (Imidacloprid-Pyriproxyfen) once topically by the owner. The cat was also bathed several times in an unknown flea shampoo and was administered a flea dip product. On 25-Jul-2012 the cat received an additional dose of Advantage II. On approximately 28-Aug-2012 the cat died. No necropsy was performed.

Assessment:
The clinical sign reported is not consistent with a topically acting product. Death is never expected following the use of any topical product. No necropsy was performed and the body has already been taken care of. Without a necropsy, it is impossible to determine what other disease process played a part in the animal's death.

2012-US0037573

Summary:
The cat was started on an unknown dose of prednisolone orally on approximately 01Aug2010. On 25Jul2012, a 15 year old, 6.5 pound, spayed, female, Domestic Shorthair, in fair condition, with a history of intestinal lymphoma, was administered 1 tube of Advantage II Small Cat (Imidacloprid-Pyriproxyfen) once topically by the owner. An undetermined amount of time later, the cat developed lameness in her hind legs. The owner declined diagnostics and treatments for the cat and elected to euthanize the cat on approximately 09Aug2012.

Assessment:
The symptom reported is not anticipated following use of this topically-applied product. It should be noted that the cat had intestinal lymphoma prior to product application. It is likely that the symptom observed was a result of that pre-existing condition, rather than related to the product. The owner elected to euthanize the cat.

2012-US0038107
Summary:
On 25-Aug-2012, an 11 year old, 9.1 pound, spayed, female, Persian feline, in fair condition, with a recent change in behavior (hiding) and flea infestation, was administered 1 tube of Advantage II Large Cat (Imidacloprid-Pyriproxyfen) once topically by the owner. 4 hours post application the cat had hind limb weakness. The cat was not seen or treated by a veterinarian. 8 hours post application the cat passed away. No necropsy was performed.

Assessment:
This is not anticipated with the proper use of the product. It is unknown what, if any, role the product played in this event. This cat had recently begun behaving abnormally, therefore, other etiologies should be considered. No necropsy examination was performed, therefore the exact cause of death cannot be determined.

2012-US0038281
Summary:
On 02-Jul-2012, a 2 year old, 8 pound, spayed, female, Domestic Mediumhair feline, in good condition, with no known concomitant medical conditions, was administered 1 tube of Advantage II Small Cat (Imidacloprid-Pyriproxyfen) once topically by the owner. On 08-Jul-2012 the pet developed respiratory distress and was examined by a veterinarian. Unknown procedures were performed and the pet was euthanized. No necropsy examination was performed.

Assessment:
The clinical sign reported is not consistent with a topically acting product. Death is never expected following the use of any topical product. No necropsy was performed and the body has already been taken care of. Without a necropsy, it is impossible to determine what other disease process played a part in the animal's death. No quality issues were noted upon product investigation.

2012-US0039042
Summary:
Due to the specifics of this case being unknown, some aspects were approximated and the case is reported as such. On approximately 01-Jul-2012, a 15 year old, Mixed Breed feline, in poor condition, with diabetes mellitus, was administered 1 tube of Advantage II Large Cat (Imidacloprid-Pyriproxyfen) once topically by the owner. On an undetermined date following the application of product the cat died due to its diabetes.

Assessment:
This feline was reported to have diabetes mellitus and died due to complications of its disease. Advantage is a safe, non-toxic product and signs of this nature would not be anticipated. The owner called to see if product could be used on her new pet and not because product caused a problem.

2012-US0039233

Summary:
On approximately 01Aug2011, a feline of unknown signalment, in unknown condition, with no known medical conditions, was administered 1 tube of Advantage II Small Cat (Imidacloprid-Pyriproxyfen) once topically by the owner. An undetermined amount of time later, the cat was euthanized. No other information was provided by the reporting party at the time of the phone call.

Assessment:
The intent of the phone call to Bayer was to ask about dosing another cat with the product and not to report the death of this patient. The product continues to be used in this home. A product investigation did not reveal any product quality issues.

2012-US0040230

Summary:
On approximately 01-Aug-2011, a 20 year old, Unknown Breed feline, in unknown condition, with no known concomitant medical conditions, was administered 1 tube of Advantage II Small Cat (Imidacloprid-Pyriproxyfen) once topically by the owner. An unknown day in January 2012 the cat was found deceased.

Assessment:
Death is never an expected outcome after the use of Advantage II. The cat was geriatric and there could have been many other contributing factors in this cat's death. Also, the death of the cat occurred several months after the last application of product. The owner called with questions regarding treatment of a new cat and mentioned that this cat was deceased.

2012-US0041358

Summary:
On 23-Aug-2012, a 5 week old, 1.4 pound, intact, male, Domestic Shorthair feline, in unknown condition, with a concomitant medical condition of a severe flea infestation, was administered 1 tube of Advantage II Kitten (Imidacloprid-Pyriproxyfen) once topically by the owner. This is an extra-label use of the product per the patient weight. On 25-Aug-2012, the patient died from anemia.

Assessment:
This product was used in an off-label manner as the patient was only 5 weeks old. Even though this was off-label, we still would not expect death after product use due to this

being a topically active product. The patient had a heavy flea infestation, which should be considered as a potential cause.

2012-US0041813

Summary:

On 08Sep2012, a 3 year old, 8 pound, male, Domestic Shorthair feline, in good condition, was administered 1 tube of Advantage II Large Cat (Imidacloprid-Pyriproxyfen) once topically by the owner. This is an overdose of the product. Within several minutes post application the patient began hypersalivating. Hypersalivation lasted approximately 3-4 hours and resolved. 10Sep2012 the patient seemed to be in pain when walking. 11Sep2012 the patient became lethargic and then was unable to be found for a few days until he was found deceased in their home on 13Sep2012. No necropsy was performed.

Assessment:

The product was used in an off label manner. The patient was given an overdose. The product has a wide margin of safety and death after use of this topically active product would not be anticipated. Death could have multiple potential causes and other etiologies cannot be ruled out. A necropsy was not performed therefore the cause of death is unable to be determined.

2012-US0042064

Summary:

On approximately 10-Jul-2012, a 8 year old, 16 pound, neutered, male, Maine Coon Cat feline, in poor condition, with concomitant medical conditions of hypertrophic cardiomyopathy and a saddle thrombus, was administered 1 tube of Advantage II Large Cat (Imidacloprid-Pyriproxyfen) once topically by the owner. Immediately after application, the patient began to "go nuts" (behavioral). On approximately 17-Jul-2012, the patient was euthanized due to the saddle thrombus.

Assessment:

The symptom reported is not anticipated following the use of this product. The patient may have been exhibiting a behavioral response to having a liquid product applied. The patient had serious concomitant illnesses and was euthanized due to the saddle thrombus. The initial contact to Bayer was to ask questions about her other cat and not to report the death of this patient.

2012-US0043484

Summary:

On approximately 01-Jul-2012, a 16 year old, unknown signalment, Domestic Shorthair feline, in unknown condition, with a concomitant medical condition of anorexia, was administered 1 tube of Advantage II Large Cat (Imidacloprid-Pyriproxyfen) once topically by the owner. On approximately 15 Jul 2012 the cat was euthanaized due to being anorexic.

Assessment:
The clinical sign reported is not consistent with a topically acting product. Death is never expected following the use of any topical product. No necropsy was performed and the body has already been taken care of. Without a necropsy, it is impossible to determine what other disease process played a part in the animal's death. The caller originally called to ask a question about our product and mentioned the cat that was euthanized.

Advantage II for Dogs Deaths for Reports with a Date First Valid between 01 Jul 2012 and 30 Sep 2012 Inclusive

*Included in the Summaries are reports not factored into statistical analysis as the products were for Advantix II (unspecified).

2012-US0028195
Summary:
Due to the nature of the communication, more specific information could not be obtained; the case will be reported with the limited information available. On an unknown date, a 17 year old, spayed female, Labrador Retriever canine, in unknown condition, with no known concomitant medical conditions, was administered 1 tube of Advantage II (dog-unspecified) (Imidacloprid-Pyriproxyfen) once topically by the owner. An unspecified amount of time after the product was applied the dog passed away from old age. No necropsy was performed.

Assessment:
The intent of the phone call to Bayer Animal Health was not to report the death of this patient and was mentioned in passing. This patient was 17 years old and died of old age. The owner did not feel the product had any relation in the pets' death and is continuing to use the product on a new pet.

2012-US0028723
Summary:
On approximately 01-Apr-2012, a 12 year old, female, Basset Hound canine, in fair condition, was administered 1 tube of Advantage II Extra Large Dog (Imidacloprid-Pyriproxyfen) once topically by the owner. The dog was diagnosed with a tumor in her mouth. The dog died on approximately 15-Apr-2012.

Assessment:
Death is never an expected outcome with the use of a topical product. The dog was diagnosed with a tumor in his mouth and the death is more than likely due to this. The caller was given three tubes of product from this dog's owner and was calling to find out if they could be used. It was only mentioned in passing that this patient was deceased.

2012-US0029680

Summary:

On approximately 01Jul2011, a canine of unknown signalment, in unknown condition, with no known medical conditions, was administered 1 tube of Advantage II Medium Dog (Imidacloprid-Pyriproxyfen) once topically by the owner.

An undetermined amount of time later, the dog passed away. No other information was provided by the reporting party.

Assessment:

The symptom reported is not anticipated following the use of this topically-applied product. No previous medical history on the dog was provided. It is unknown what, if any, medical conditions the dog had at the time the product was applied. Therefore, other etiologies must be considered. The intent of the call to Bayer was to ask if the remaining product could be used on a new pet, and not to report the death of the patient or any adversity with the product.

2012-US0030637

Summary:

On 04-Jul-2012, a 12 year old, 41 pound, neutered, male, Chowchow canine, in unknown condition, with a history of fleas and had not been seen by the veterinarian for **6** years, was administered 1 tube of Advantage II Large Dog (Imidacloprid-Pyriproxyfen) once topically by the owner. Product was applied entirely at one area at the base of the neck. On 9-Jul-2012 pet developed hair loss at the application site on the neck and on the caudodorsum. On 10-Jul-2012 skin lesions developed in the affected areas of hair loss. This developed into necrotic tissue on approximately 11-Jul-2012. On 13-Jul-2012 the dog was examined by a veterinarian, and prescribed Cephalexin 500mg twice daily and silversulfasalazine topical cream. On 18-Jul-2012 the patient was re-examined and prescribed prednisone 20mg one time daily on a decreasing dose. 21-Jul-2012 this patient passed away. No necropsy was performed.

Assessment:

This dog had not been seen by the veterinarian for the past 6 years, therefore the state of its medical health was unknown. Other etiologies should be considered. The cause of the necrotic skin at the application site was not determined. The extent of the clinical signs reported and ultimate outcome of this patient is not fitting with the properties of the product. No necropsy was performed therefore the exact cause of death is unknown.

2012-US0032371

Summary:

On 16Jul2012, an 8 year old, 54.7 pound, intact, male, Labrador Retriever crossbred canine, in good condition, with no known medical conditions, was administered the following vaccines: Rabies, Distemper, and Bordetella. A heartworm test was negative (normal). On 17Jul2012, the dog was administered 1 tablet of milbemycin oxime once orally by the owner. On 18Jul2012, the dog was administered 1 tablet of acepromazine maleate once orally by the owner. After that, the dog received 1 tube of Advantage II

Large Dog (Imidacloprid-Pyriproxyfen) once topically by the owner. Several hours later, the dog passed away.

Assessment:
This patient received multiple medications prior to administration of Advantage II. The medical condition for which the acepromazine was administered is unknown. No necropsy results are available to determine the cause of death. No quality issues were noted upon product investigation. What role, if any, the product played in this case cannot be determined.

2012-US0035651

Summary:
On 01-Feb-2012, a 13 year old, 50 pound, male, Golden Retriever Mix canine, in poor condition, was administered 1 tube of Advantage II Large Dog (Imidacloprid-Pyriproxyfen) once topically by the owner. The dog has a history of renal insufficiency and was on dialysis. On 15-May-2012 the dog had a severe seizure. The owner presented the dog to the veterinarian and euthanasia was elected.

Assessment:
Death is never an expected outcome from a topically applied product. The dog had a history of renal failure and when the dog had a severe seizure the owners elected euthanasia. The owner called only to ask if this box of product could be used on another dog that she has.

2012-US0036285

Summary:
On 15-Jul-2012, a 10 year old, 75 pound, spayed, female, English Bulldog canine, in good condition, with a history of entropion and bladder stones, was administered 1 tube of Advantage II Extra Large Dog (Imidacloprid-Pyriproxyfen) once topically by the owner. Approximately 3 hours after application of the product the dog began vomiting. One hour after that the dog stood up and died. A necropsy was not performed.

Assessment:
Death is never an expected outcome from the application of a topical product. No necropsy was performed so cause of death could not be determined. This product is safe and non-toxic and death would not be anticipated. The initial call into Bayer Animal Health was to inquire about using the product on a new pet and not to report the death of this pet.

2012-US0036376

Summary:
On an unknown date approximately March 2011, a 11 year old, 92 pound, neutered, male, Retriever Labrador (No Description)/Rottweiler crossbred canine, in good condition, with no known concomitant medical conditions, was administered 1 tube of Advantage II (dog-unspecified) (Imidacloprid-Pyriproxyfen) once topically by the owner.

On 11-Jun-2012 the dog passed away due to old age. No treatments were performed. The dog was not seen by a veterinarian. No necropsy was performed.

Assessment:
The owner initially contacted Bayer Animal Health to seek advice on how to control an active flea infestation and not to report the death of this pet. Due to the long duration of the time to onset of this patient's death from when the product was used, it is very unlikely that the product has any relation to the patient's death. No necropsy was performed so it is impossible to determine the exact cause of death.

2012-US0036378
Summary:
On an unspecified date approximately May-2012, a 7.5 year old, 134 pound, intact, male, Rottweiler canine, in good condition, with no known concomitant medical conditions, was administered 1 tube of Advantage II (dog-unspecified) (Imidacloprid-Pyriproxyfen) once topically by the owner. On 13-Jul-2012 the dog passed away, presumably, from a blood clot. It is unknown if the dog was seen or treated by a veterinarian. No necropsy was performed.

Assessment:
The owner initially contacted Bayer Animal Health to seek advise on how to control an active flea infestation and not to report the death of this pet. Due to the long duration of the time to onset of this patient's death from when the product was used, it is very unlikely that the product has any relation to the patient's death. No necropsy was performed so the exact cause of death is unknown.

2012-US0036472
Summary:
On 01-Jun-2012, a 9 year old, 85 pound, intact, male, Pit Bull canine, in poor condition, with a known medical history of heart worms, was administered 1 tube of Advantage II Extra Large Dog (Imidacloprid-Pyriproxyfen) once topically by the owner. On 22-Jun-2012 the pet passed away.

Assessment:
Due to the concomitant medical conditions of heart worm disease that this pet was diagnosed with, it is unlikely that a topically acting product was related to the death of the patient.

2012-US0037452
Summary:
On approximately 07Aug2012, a 9 year old, 8 pound, female, Miniature Pinscher, in good condition, with no known medical conditions, was administered 1 tube of Advantage II Small Dog (Imidacloprid-Pyriproxyfen) once topically by the owner. That night, the dog slept in bed with the owner. The morning of 08Aug2012, the dog was unable to walk and her whole body was shaking. The owner bathed the dog with an herbal shampoo. The dog was seen at the veterinary clinic and sent home with pain pills

and anti-inflammatory pills. The symptoms continued. The owner declined any other diagnostics and treatments for the dog and elected to euthanize her on approximately 24Aug2012.

Assessment:
The symptom observed is not anticipated following the use of this topically-applied product. It should be noted that the dog was a dachshund; it is not unusual for dachshunds to experience back injuries. No quality issues were noted upon product investigation. The owner declined diagnostics and treatments and elected to euthanize the dog instead.

2012-US0040984
Summary:
On an unspecified date in June of 2007, a 14 year old, 20 pound, neutered, male, Schnauzer (Miniature) canine, in fair condition, with a known medical history of kidney stones, was administered 1 tube of Advantage II Small Dog (Imidacloprid-Pyriproxyfen) once topically by the owner. On an unspecified date in December of 2007 the dog was euthanized due to kidney stones.

Assessment:
This patient was euthanized due to complications associated with a pre-existing condition.

2012-US0040985
Summary:
On 05-Sep-2012, a 2 year old, 10 pound, intact, female, Pomeranian canine, in good condition, with no known concomitant medical conditions, was administered 1 tube of Advantage II Small Dog (Imidacloprid-Pyriproxyfen) once topically by the owner. On 07-Sep-2012 the dog became ataxic, began vomiting, became inappetant, and was vocalizing. On 08-Sep-2012 the dog became lethargic. The dog presented to the veterinarian. Upon examination the dog was also tachycardic and hypothermic. The dog was given subcutaneous fluids and activated charcoal. The owner declined all other treatments and blood work. The signs continued. On 08-Sep-2012 the dog was bathed with no resolution of symptoms. On 09-Sep-2012 the dog presented again to the veterinarian having grand mal seizures. The dog was then euthanized. No necropsy was performed.

Assessment:
Death is never an expected outcome from the use of a topical product. Advantage II is a safe, non-toxic product and signs of this nature would not be anticipated. The dog presented to the veterinarian 4 days after product application having grand mal seizures. No diagnostics were performed and the dog was euthanized due to financial concerns. No necropsy was performed.

2012-US0041988

Summary:

On 16-Sep-2012, a 2 year old, 8 pound, intact female, Dachshund canine, in good condition, with a current flea infestation and mild dermatitis, was administered 1 tube of Advantage II Small Dog (Imidacloprid-Pyriproxyfen) once topically by the owner. Approximately three hours after product application the dog developed a behavioral changed and appeared agitated. She also had abnormal respiration. The dog then became ataxic began retching and was lethargic. Later in the night the dog began yelping. On the morning of 17 Sept 2012 the dog was found deceased. The results of the necropsy: 1.) Hiatal hernia with jejunal and gastric entrapment. 2.) Flea infestation with mild dermatitis.

Assessment:

A necropsy was performed and revealed the cause of death was due to a hiatal hernia with jejunal and gastric entrapment. No quality issues were noted upon product investigation.

2012-US0043058

Summary:

On approximately 21-Sep-2011, a 10 year old, 90 pound, female, Retriever Labrador (No Description) canine, in poor condition, with a concomitant medical condition of cancer, was administered 1 tube of Advantage II (unspecified) (Imidacloprid-Pyriproxyfen) once topically by the owner. On approximately 07-Sep-2012 the dog was euthanized due to the cancer. No treatments were performed.

Assessment:

The owner initially contacted Bayer Animal Health to seek advise on how to control an active flea infestation and not to report the death of this pet. Due to the long duration of the time to onset of this patient's death from when the product was used, it is very unlikely that the product has any relation to the patient's death.

2012-US0043494

Summary:

On 21-Sep-2012, a 8 year old, 60 pound, spayed female, German Shepherd Dog canine, in good condition, with a current flea infestation and bacterial otitis externa, was administered 1 tube of Advantage II Extra Large Dog (Imidacloprid-Pyriproxyfen) once topically by the owner. On 22 Sept 2012 the dog underwent a behavioral change (reclusive toward owner, digging holes in the yard and laying in them) and became anorexic. She then began vomiting and later that day passed away. The dog was not seen by a veterinarian for the clinical signs. No necropsy was performed.

Assessment:

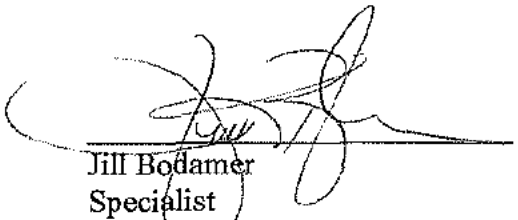
The clinical signs exhibited up to and including death are not indicative of toxicity associated with imidacloprid or pyriproxyfen. The exact cause of death could not be determined. What role, if any, the product played in this case also cannot be determined.

We believe this summary of data meets the requested information in the Agency's requirements for enhanced reporting as outlined in its January 19, 2011 communication to Bayer.

A report with the confidential sales information and additional analysis of incident rates based on doses sold is being sent to the Registration Division, Immediate Office (attn. Ms. Kimberly Nesci).

If there are any questions regarding this submission, please contact me by phone at 913.268.2082 or by e-mail at jill.bodamer@bayer.com.

Most Kind Regards,



Jill Bodamer
Specialist
Regulatory Affairs

Bayer HealthCare

April 25, 2012

Document Processing Desk
Office of Pesticide Programs (7540P) - Non PRIA
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Attention: Ms. Venus Eagle (PM/01)

Subject: Amended Submission for:
Advantage II Small Cat (EPA Reg. No. 11556-151)
Advantage II Large Cat (EPA Reg. No. 11556-152)
Advantage II Medium Dog (EPA Reg. 11556-125)

An internal audit of our reporting procedure for the conditional registration requirement of enhanced quarterly incident reporting found that, in some instances, reports were duplicated causing incident report numbers to be over-reported in previous submissions. The affected products have been identified and amended in this submission

This submission includes the following tables covering cumulative incident reporting from January 1, 2011 through December 31, 2011:

Summary Table
Breed Summary
Age Range Summary
Clinical Signs Summary
Organ System Summary
Patient Weight Range Summary
Product Weight Range Summary
Route of Exposure Summary
Secondary Exposure Summary

Due to the length of the tables and to provide the Agency with the ability to sort, this data is being provided electronically on a CD. The data was extracted from Bayer's Pharmacovigilance data base (PV Works). The root cause of the duplication of reports has been addressed and should not be an issue in future submissions.

Deaths
There were no duplications of reports involving death in Advantage II Small Cat, Advantage II Large Cat, or Advantage II Medium Dog.

Bayer HealthCare

An amended report, along with the related sales information and analysis of incident rates based on doses sold of the affected products is being sent to the Registration Division, Immediate Office (attn. Ms. Kimberly Nesci).
If there are any questions regarding this submission, please contact me by phone at 913.268.2982 or by email at jill.bodamer@bayer.com.

Jill Bodamer
Specialist
Regulatory Affairs

Bayer HealthCare
Animal Health Division

August 31, 2011,

Document Processing Desk
Office of Pesticide Programs (7504P) – NonPRIA
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Attention: Ms. Venus Eagle/PM01

Subject: Advantage II Kitten (EPA Reg. No. 11556-150)
Advantage II Small Cat (EPA Reg. No. 11556-151)
Advantage II Large Cat (EPA Reg. No. 11556-152)
Advantage II Small Dog (EPA Reg. No. 11556-128)
Advantage II Medium Dog (EPA Reg. No. 11556-125)
Advantage II Large Dog (EPA Reg. No. 11556-127)
Advantage II Extra Large Dog (EPA Reg. No. 11556-130)

Please find enclosed the conditional registration requirement of enhanced quarterly incident report for Advantage II Dog and Cat registrations for the quarter starting April 1, 2011.

This submission includes the following tables covering incident reporting from April 01, 2011 through June 30, 2011:

Summary Table (multiple pages due to length)
Breed Summary
Age Range Summary
Clinical Signs Summary
Organ System Summary
Patient Weight Range Summary
Product Weight Range Summary
Route of Exposure Summary
Secondary Exposure Summary

Due to the length of some of the tables and to provide the Agency the ability to sort, this data is being provided electronically on a CD. The data was extracted from Bayer's pharmacovigilance data base (P.V. Works).

Deaths

Deaths were reported in four (4) felines that had previously received treatment with Advantage II during the period of review. Specifics are as follows:

2011-US0010189

Summary:

A 4 week old kitten of unknown weight with a heavy flea infestation and ocular discharge was nursing from a queen that was a stray with mastitis. The kitten had been administered amoxicillin, an eye ointment for ocular discharge and formula (unspecified) starting on 12April11. The queen had a partial tube of Advantage II Large Cat applied to her on 16April11 for a current flea infestation. On the morning of 17April11 the owner states the kitten appeared to take a turn for the worse. By that evening the kitten seemed cold and died in the owners arms. No necropsy examination was performed.

Assessment:

Imidacloprid, the active ingredient in Advantage is non-toxic and would not be expected to cause death or any other systemic effects. The product was applied to the queen and not to the kitten. As the kittens had a heavy flea infestation and were being treated with other medications for ocular discharge before the Advantage was used, it is unknown what part the other medications and formula played in this case. As the attending veterinarian is suspecting a metabolic disease, other etiologies must be considered in this case. It was also noted the kitten was nursing from a queen with mastitis, most likely ingesting infectious organisms during the process.

2011-US0017230

Summary:

On 12May2011 owner applied monthly dose of Advantage II Large Cat to

Slim, a 7 year old neutered male Domestic Short hair that weighs 10 pounds. 10 days later, on 22May2011 this feline collapsed. On 23May2011 the doctor examined and found this feline was very jaundiced. The cat went in to cardiac arrest and passed away while the veterinarian was obtaining blood for testing. Blood work showed what the attending veterinarian believed to be full organ function failure. Results were: Lymphocytes % low at 7.5% (12-45), Granulocyte % High at 86 (35-80), RBC High at 11.71 (4.6-10), HCT high at 50.8 % (28-49), MCH low at 12..4 pg (13-21), MCHC low at 28.7 g/dL (30-38), PLT low at 92 (100-514), ALP low <5 (10-90), ALT High 205 (20-100), TBIL High 10.8 (0.1-0.6), BUN High 82 (10-30), CA High 11.9 (8.0-11.8), PHOS High 11.2 (3.4-8.5), Glu low 57 (70-150), TP High 9.4 (5.4-8.2), and GLOB High 6.0 (1.5-5.7)
No necropsy was preformed.

Assessment:
These clinical signs are non-specific and may have multiple potential other causes. Imidacloprid and pyriproxyfen are the active ingredients of the topical acting product Advantage II Large cat. This feline present to the veterinarian 12 days after application in full organ failure. The attending veterinarian does not believe was product-related. The lot investigations showed no product quality issue evident. No necropsy was performed.

2011-US0018883
Summary:
Advantage II Small Cat was applied for the first time to a 10 year old, approximately 8.5 pound Domestic Shorthair on 29May11. The evening of 31May11, the owner came home from work to find her cat dead in the bathroom. No necropsy was performed.

Assessement:
The clinical sign reported is not consistent with a topically acting product. Death is never expected following the use of any topical product. Without a necropsy, it is impossible to determine the cause of death. QA investigation results did not reveal any product abnormalities.

Bayer HealthCare
Animal Health Division

2011-US0021320

Summary:
Owner treated a 12 year old, 4 pound, female cat with half a tube of Advantage II Large Cat and this cat immediately disappeared after application. Caller found cat dead in the back yard seven days later. No necropsy examination was performed.

Assessment:
Product was used in an off-label manner, however death after product use is not consistent with active ingredient. No necropsy was performed and it is unknown what else the cat may have been exposed to for those seven days prior to death.

We believe this summary of data meets the requested information in the Agency's requirements for enhanced reporting as outlined in its January 19, 2011 communication to Bayer.

A report with the confidential sales information and additional analysis of incident rates based on doses sold is being sent to the Registration Division, Immediate Office (attn. Ms. Kimberly Nesci).

If there are any questions regarding this submission, please contact me by phone at 913.268.2573 or by e-mail at gary.brumley@bayer.com.

Gary Brumley
Senior Consultant
Regulatory Affairs

Material Sent for Data Extraction

Reg. # 11556-151

Description: Amend

☒ Material(s) Sent to Data Extraction Contractors:

- ☑ New Stamped Label Dated 3/28/13
- ☐ Notification Dated _____
- ☐ New CSF(s) Dated _____
- ☐ Other: _____

☐ Decision #: _____

☐ Other Action/Comments: _____

_____

File this coversheet and attached materials in the jacket. It must be well organized and clipped together, NOT STAPLED. Then give the jacket with the coversheet and materials to staff in the Information Services Center (ISC) (Room S-4900). If a jacket is full or only available as an image, please file materials in a new jacket and bring it down to the (ISC). For further information please call 703-605-0716.

Reviewer: Jennifer Urbanski

Phone: 347-0156 Division: RD

Date: 3/28/13

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

Douglas Spilker
Bayer HealthCare LLC, Animal Health Division
PO Box 390
Shawnee Mission, KS 66201

Dear Mr. Spilker:

MAR 2 8 2013

Subject: Amendments to add new child resistant packaging
Advantage II Small Cat
EPA Registration No. 11556-151
Decision Numbers: 473349
Submission Dates: December 14, 2012

The label referred to above, submitted in connection with registration under the Federal Insecticide, Fungicide, and Rodenticide Act, as amended, is acceptable. A stamped copy of the label is enclosed for your records. Please submit two copies of your final printed labeling before you release the product for shipment. If you have any questions regarding these labels, please contact Dr. Jennifer Urbanski at 703-347-0156 or urbanski.jennifer@epa.gov.

Sincerely yours,

Venus Eagle
Product Manager (01)
Insecticide-Rodenticide Branch
Registration Division (7505P)

Enclosure- Stamped Label and Science Reviews (DP408179)

Reason To Issue: New child-resistant packaging proposal. Date: 02/14/13
Supersedes: 12/12/12, 11/28/12 and 11/07/12

NOTE TO REVIEWER: [(Brackets and parentheses indicate alternate language)]

[Front Panel]

Advantage® II Small Cat

Once-A-Month Topical Flea Prevention and Treatment for Cats and Ferrets
For Use ONLY on Cats 8 Weeks and Older and Weighing 5 - 9 lbs. or Ferrets 10 weeks and Older and Weighing 1 lb. or Greater

[Selected optional claims bulleted here from page 11 and/or 12]

-
-
-
-

Active Ingredients	% By Weight
Imidacloprid	9.10%
Pyriproxyfen	0.46%
Other Ingredients	90.44%
Total	100.00%

EPA Est. No. 11556-XXX-X EPA Reg No. 11556-151

KEEP OUT OF REACH OF CHILDREN

CAUTION

See back panel for Precautionary Statements.
For Directions for Use, Storage and Disposal, and First Aid see package insert inside.

ACCEPTED
MAR 2 6 2013
Under the Federal Insecticide, Fungicide, and Rodenticide Act, as amended, for the pesticide registered under:
EPA. Reg. No: 11556-151

[Back Panel]

Advantage® II Small Cat

Once-A-Month Topical Flea Prevention and Treatment for Cats and Ferrets
For Use ONLY on Cats 8 Weeks and Older and Weighing 5 - 9 lbs. or
Ferrets 10 weeks and Older and Weighing 1 lb. or Greater

READ THE ENTIRE LABEL BEFORE EACH USE
For the Prevention and Treatment of Flea Infestations

PRECAUTIONARY STATEMENTS
HAZARDS TO HUMANS

CAUTION: Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling. Keep out of reach of children. Do not contaminate feed or food.

HAZARDS TO DOMESTIC ANIMALS

For external use only. Do not apply to cats or kittens under 8 weeks of age or weighing less than 5 lbs. or on kits (young ferrets) under 10 weeks of age or weighing less than 1 lb. As with any product, consult your veterinarian before using this product on debilitated, aged, pregnant or nursing cats [or ferrets. Individual sensitivities, while rare, may occur after using ANY pesticide product for cats or ferrets. If signs persist, or become more severe, consult a veterinarian immediately. If your cat or ferret is on medication, consult your veterinarian before using this or any other product.

Side Effects (Cats): Monitor your cat after application. Side effects, although very rare, may include signs of skin irritation such as redness, scratching, or other signs of discomfort. Gastrointestinal signs such as hypersalivation, vomiting or diarrhea have also been reported. If these or other side effects (such as lethargy) occur, consult your veterinarian or call 1-800-422-9874.
Side Effects (Ferrets): Monitor your ferret after application. Side effects, although very rare, may include temporary changes in fecal consistency. If these or other side effects occur, consult your veterinarian or call 1-800-422-9874.

For consumer questions call 1-800-255-6826.
For medical emergencies call 1-800-422-9874.

RESTRICTIONS:

- Use only on cats or kittens 8 weeks and older and weighing 5 – 9 lbs. and only on ferrets 10 weeks and older and weighing 1 lb. or greater. Do not use on other animals.
- Do not apply more than one (1) tube per treatment.

- Do not have contact or allow children to have contact with treated area until completely dry.

Net Contents: [X] Tube(s), each 0.014 fl. oz. (0.4 mL)

[Sample - Not for (Re)Sale]

Manufactured For

Bayer HealthCare LLC
Animal Health Division
P.O. BOX 390
Shawnee Mission, Kansas 66201 USA

Made in Germany

[Back Panel and/or Insert]

Advantage® II Small Cat

Once-A-Month Topical Flea Prevention and Treatment for Cats and Ferrets
For Use ONLY on Cats 8 Weeks and Older and Weighing 5 - 9 lbs. or
Ferrets 10 weeks and Older and Weighing 1 lb. or Greater

READ THE ENTIRE LABEL BEFORE EACH USE
For the Prevention and Treatment of Flea Infestations

DIRECTIONS FOR USE

It is a violation of Federal Law to use this product in a manner inconsistent with its labeling.

HOW TO OPEN

[OPTION 1: INSTRUCTIONS FOR BLISTER PACK]
1. Being careful not to cut close to the blister cavities, take scissors and cut off one section of the card containing a single tube.
2. Take the separated section, and cut into the blister cavity across the small side, close to the cap of the tube.
3. Peel off the foil, and take out the tube.
4. Repeat steps 1 to 3 for each tube.

[OPTION 2: INSTRUCTIONS FOR POUCH PACK]
1. Be sure tube is at bottom of pouch.
2. Using scissors, cut the pouch across the top and remove tube.

HOW TO APPLY

1. Remove one applicator tube from the package. See "HOW TO OPEN" section.
2. Hold applicator tube in an upright position facing away from you and your pet's face and eyes. Pull cap off tube.

[Visuals Depicting How to Open Applicator Tube]

3. Turn the cap around and place other end of cap back on tube.

4. Twist cap to break seal, then remove cap from tube.
5. Part the hair on the neck at the base of the skull until the skin is visible. Place the tip of the tube on the skin and squeeze the tube to expel the entire contents directly on the skin. *Do not get this product in your pet's eyes, or allow your pet to ingest this product. The product is bitter tasting and salivation may occur for a short time if the pet licks the product immediately after treatment.* Treatment at the base of the skull will minimize the opportunity for the cat to lick the product. Do not allow the product to run off.

[2 Separate Visuals (1 cat; 1 ferret) depicting Application to the Animals]

6. Discard empty tube as described in Storage and Disposal.
7. Under normal conditions this product is effective for a month. However, in case of severe flea infestation, retreatment may be necessary earlier than four (4) weeks. On cats, do not retreat more often than once every seven (7) days. On ferrets, do not retreat more often than every 14 days. After flea control is attained, return to a monthly retreatment schedule.

PRODUCT INFORMATION FOR CATS

The successive feeding activity of fleas on cats frequently elicits a hypersensitivity skin disorder known as flea allergy dermatitis (FAD) or flea bite hypersensitivity. Treatment of cats with Advantage® II Small Cat kills fleas and may reduce the incidence of this condition.

Advantage® II Small Cat kills the existing fleas on cats within 12 hours. Reinfesting fleas are killed within 2 hours with protection against further flea infestation lasting for up to four (4) weeks. Pre-existing pupae in the environment may continue to emerge for six (6) weeks or longer depending upon the climatic conditions.

Fleas, eggs and larvae in the cat's surroundings are killed following contact with an Advantage® II Small Cat treated cat. Advantage® II Small Cat provides multi-stage flea control effectively breaking all flea life-cycle stages for lasting control of flea populations.

Advantage® II Small Cat kills adult fleas quickly, within 12 hours, inhibits the development of immature flea life stages and prevents them from reaching the biting adult stage.

Advantage® II Small Cat is waterproof and remains effective following a shampoo treatment or after exposure to rain or sunlight.

Apply monthly treatments for optimal control and prevention of fleas.

PRODUCT INFORMATION FOR FERRETS

Advantage® II Small Cat kills the existing fleas on ferrets within 24 hours. Reinfesting fleas are killed with protection against further flea infestation lasting for up to four (4) weeks. Pre-existing pupae in the environment may continue to emerge for six (6) weeks or longer depending upon the climatic conditions.

Fleas, eggs and larvae in the ferret's surroundings are killed following contact with an Advantage® II Small Cat treated ferret. Advantage® II Small Cat provides multi-stage flea control effectively breaking all flea life cycle stages for lasting control of flea populations.

Advantage® II Small Cat kills adult fleas within 24 hours, inhibits the development of immature flea life stages and prevents them from reaching the biting adult stage.

Advantage® II Small Cat is waterproof and remains effective following a shampoo treatment or after exposure to rain or sunlight.

Apply monthly treatments for optimal control and prevention of fleas.

KEEP OUT OF REACH OF CHILDREN

CAUTION

PRECAUTIONARY STATEMENTS
HAZARDS TO HUMANS

CAUTION: Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling. Keep out of reach of children. Do not contaminate feed or food.

FIRST AID	
If Swallowed:	• Call a poison control center or doctor immediately for treatment advice. • Have person sip a glass of water if able to swallow. • Do not induce vomiting unless told to do so by the poison control center or doctor. • Do not give anything to an unconscious person.
If In Eyes:	• Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. • Call a poison control center or doctor for treatment advice.
If On Skin	• Wash with plenty of soap and water.
HOT LINE NUMBER	
Have the product container or label with you when calling a poison control center or doctor, or going for treatment. For medical emergencies call 1-800-422-9874. For customer questions call 1-800-255-6826.	
NOTE TO PHYSICIAN	
Treat the patient symptomatically.	

HAZARDS TO DOMESTIC ANIMALS

For external use only. Do not apply to cats or kittens under 8 weeks of age or weighing less than 5 lbs. or on kits (young ferrets) under 10 weeks of age or weighing less than 1 lb. As with any product, consult your veterinarian before using this product on debilitated, aged, pregnant or nursing cats or ferrets. Individual sensitivities, while rare, may occur after using ANY pesticide product for cats or ferrets. If signs persist, or become more severe, consult a veterinarian immediately. If your cat or ferret is on medication, consult your veterinarian before using this or any other product.

Side Effects (Cats): Monitor your cat after application. Side effects, although very rare, may include signs of skin irritation such as redness, scratching, or other signs of discomfort. Gastrointestinal signs such as hypersalivation, vomiting or diarrhea have also been reported. If these or other side effects (such as lethargy) occur, consult your veterinarian or call 1-800-422-9874.
Side Effects (Ferrets): Monitor your ferret after application. Side effects, although very rare, may include temporary changes in fecal consistency. If these or other side effects occur, consult your veterinarian or call 1-800-422-9874.

For consumer questions call 1-800-255-6826.
For medical emergencies call 1-800-422-9874.

RESTRICTIONS:

- Use only on cats or kittens 8 weeks and older and weighing 5 – 9 lbs. and only on ferrets 10 weeks and older and weighing 1 lb. or greater. Do not use on other animals.
- Do not apply more than one (1) tube per treatment.
- Do not have contact or allow children to have contact with treated area until completely dry.

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal.

Pesticide Storage: Store in a cool, dry place inaccessible to children and pets. **Pesticide Disposal and Container Handling:** Nonrefillable container. **If empty:** Do not reuse or refill this container. Place in trash or offer for recycling if available. **If partly filled:** Call your local solid waste agency or 1-800-422-9874 for disposal instructions. Never place unused product down any indoor or outdoor drain.

LIMITED WARRANTY AND LIMITATION OF DAMAGES

Bayer HealthCare LLC, Animal Health Division warrants that this material conforms to the chemical description on the label. TO THE EXTENT CONSISTENT WITH APPLICABLE LAW, BAYER MAKES NO OTHER EXPRESS OR IMPLIED WARRANTY, INCLUDING ANY OTHER EXPRESS OR IMPLIED WARRANTY OF FITNESS OR MERCHANTABILITY, and no agent of Bayer is authorized to do so except in writing with a specific reference to this warranty. Any damages arising from a breach of this warranty shall be limited to direct damages and shall not include consequential commercial damages such as loss of profits or values, etc.

For more information visit www.petparents.com

[Label on Individual Tube]

Advantage® II Small Cat

9.10% Imidacloprid

0.46% Pyriproxyfen

0.014 fl. oz. (0.4 mL)

EPA Reg. No. 11556-151

Keep Out of Reach of Children

CAUTION

Read The Entire Label Before Use

BAYER

Lot No. 0000000

[OPTION 1: Label on blister card; one card containing 1, 2, 3, 4, 5, or 6 tubes]
[OPTION 2: Label on pouch containing one tube]

[Additional label text for OPTION 2: THIS UNIT NOT FOR RETAIL SALE]

Advantage® II Small Cat

For external use only on cats and kittens 8 weeks and older and weighing 5 - 9 lbs.
or ferrets 10 weeks and older and weighing 1 lb. or greater

9.10% Imidacloprid

0.46% Pyriproxyfen

[X] - 0.014 fl. oz. (0.4 mL) Tube(s)

EPA Reg. No. 11556-151

BAYER

NOTE TO REVIEWER: [(Brackets and parentheses indicate alternate language)]

OPTIONAL MARKETING CLAIMS [Appearing on any panel]

- For use on cats and kittens 8 weeks of age and older
- For use on ferrets and (and kits) 10 weeks of age and older
- Advantage II contains [imidacloprid], [and an/the] [insect growth regulator] [IGR] [pyriproxyfen]
- A single topical application remains effective for up to [4 weeks] [a month]
- Convenient, easy-to-apply topical solution
- Convenient, easy-to-apply and fragrance free [monthly] [topical solution]
- Once a month topical flea prevention and treatment for cats 8 weeks of age or older [and ferrets 10 weeks of age and older]
- Advantage II is indicated for the prevention and treatment of fleas on cats 8 weeks of age and older [and ferrets 10 weeks of age and older]
- For the prevention and treatment of flea infestations
- One treatment prevents further flea infestations for up to [4 weeks] [a month]
- Kills fleas within 12 hours on cats [, 24 hours on ferrets,] and continues to prevent infestations for up to [four weeks] [a month]
- Kills fleas before they lay eggs
- Larval flea stages in the pet's environment are killed following contact with an Advantage II treated cat [or ferret]
- Kills larval stages of fleas following contact with an Advantage II treated cat [or ferret]
- Kills fleas on cats within 12 hours [and on ferrets within 24 hours] of application
- Stops existing flea infestations by killing adult fleas
- Prevents reinfestations by killing adult fleas before they lay eggs
- Reinfesting fleas on cats are killed within 2 hours with protection against further flea infestation
- [Prevents] [Stops] flea eggs from hatching [into biting adults]
- Effectively breaks the flea life cycle
- [Kills] [Controls] all flea life stages
- Comprehensive flea prevention and treatment
- 3-way flea protection ([kills] [controls]) adults, larvae, and eggs
- [Prevents] [Stops] flea eggs from developing into [(biting) (adult)] fleas
- Treatment of cats with Advantage II kills fleas and may reduce the incidence of flea allergic dermatitis [FAD] or flea bite hypersensitivity
- Flea adulticide, larvicide, and ovicide
- Kills flea eggs
- Controls flea problems
- Provides flea protection

- Controls existing fleas and flea eggs plus [and] [prevents] future flea infestations
- Advantage II may be used year-round for flea [prevention][protection]
- Contains an insect growth regulator (IGR) to kill flea eggs and prevent re-infestation
- Monthly use of Advantage II on cats kills fleas and may prevent ([flea allergy dermatitis][flea bite hypersensitivity])
- Controls existing flea infestations on your cat [or ferret] and prevents further infestations
- Prevents fleas on treated cats [or ferrets] from infesting (reinfesting)
- Remains effective after bathing
- Remains effective following shampooing
- Waterproof
- Remains effective after exposure to rain or sunlight
- Fragrance-free
- In child-resistant packaging
- Starts working through contact

Reason To Issue: New child-resistant packaging proposal. Date: 02/14/13
Supersedes: 12/12/12, 11/28/12 and 11/07/12

SUBSET LABELING: Cat Only Product
NOTE TO REVIEWER: [(Brackets and parentheses indicate alternate language)]

[Front Panel]

Advantage® II Small Cat

Once-A-Month Topical Flea Prevention and Treatment for Cats
For Use ONLY on Cats 8 Weeks and Older and Weighing 5 - 9 lbs.

[Selected optional claims bulleted here from page 10 and/or 11]

-
-
-
-

Active Ingredients	% By Weight
Imidacloprid	9.10%
Pyriproxyfen	0.46%
Other Ingredients	90.44%
Total	100.00%

EPA Est. No. 11556-XXX-X EPA Reg No. 11556-151

KEEP OUT OF REACH OF CHILDREN

CAUTION

See back panel for Precautionary Statements.
For Directions for Use, Storage and Disposal, and First Aid see package insert inside.

[Back Panel]

Advantage® II Small Cat

Once-A-Month Topical Flea Prevention and Treatment for Cats
For Use ONLY on Cats 8 Weeks and Older and Weighing 5 - 9 lbs.

READ THE ENTIRE LABEL BEFORE EACH USE
For the Prevention and Treatment of Flea Infestations

PRECAUTIONARY STATEMENTS

HAZARDS TO HUMANS

CAUTION: Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling. Keep out of reach of children. Do not contaminate feed or food.

HAZARDS TO DOMESTIC ANIMALS

For external use only. Do not apply to cats or kittens under 8 weeks of age or weighing less than 5 lbs. As with any product, consult your veterinarian before using this product on debilitated, aged, pregnant or nursing cats. Individual sensitivities, while rare, may occur after using ANY pesticide product for cats. If signs persist, or become more severe, consult a veterinarian immediately. If your cat is on medication, consult your veterinarian before using this or any other product.

Side Effects: Monitor your cat after application. Side effects, although very rare, may include signs of skin irritation such as redness, scratching, or other signs of discomfort. Gastrointestinal signs such as hypersalivation, vomiting or diarrhea have also been reported. If these or other side effects (such as lethargy) occur, consult your veterinarian or call 1-800-422-9874.

For consumer questions call 1-800-255-6826.
For medical emergencies call 1-800-422-9874.

RESTRICTIONS:

- Use only on cats or kittens 8 weeks and older and weighing 5 – 9 lbs. Do not use on other animals.
- Do not apply more than one (1) tube per treatment.
- Do not have contact or allow children to have contact with treated area until completely dry.

Net Contents: [X] Tube(s), each 0.014 fl. oz. (0.4 mL)

[Sample - Not for (Re)Sale]

Manufactured For

Bayer HealthCare LLC
Animal Health Division
P.O. BOX 390
Shawnee Mission, Kansas 66201 USA

Made in Germany

[Back Panel and/or Insert]

Advantage® II Small Cat

Once-A-Month Topical Flea Prevention and Treatment for Cats
For Use ONLY on Cats 8 Weeks and Older and Weighing 5 - 9 lbs.

READ THE ENTIRE LABEL BEFORE EACH USE
For the Prevention and Treatment of Flea Infestations

DIRECTIONS FOR USE

It is a violation of Federal Law to use this product in a manner inconsistent with its labeling.

HOW TO OPEN

[OPTION 1: INSTRUCTIONS FOR BLISTER PACK]

1. Being careful not to cut close to the blister cavities, take scissors and cut off one section of the card containing a single tube.
2. Take the separated section, and cut into the blister cavity across the small side, close to the cap of the tube.
3. Peel off the foil, and take out the tube.
4. Repeat steps 1 to 3 for each tube.

[OPTION 2: INSTRUCTIONS FOR POUCH PACK]

1. Be sure tube is at bottom of pouch.
2. Using scissors, cut the pouch across the top and remove tube.

HOW TO APPLY

1. Remove one applicator tube from the package. See "HOW TO OPEN" section.
2. Hold applicator tube in an upright position facing away from you and your pet's face and eyes. Pull cap off tube.

[Visuals Depicting How to Open Applicator Tube]

3. Turn the cap around and place other end of cap back on tube.
4. Twist cap to break seal, then remove cap from tube.

5. Part the hair on the neck at the base of the skull until the skin is visible. Place the tip of the tube on the skin and squeeze the tube to expel the entire contents directly on the skin. *Do not get this product in your cat's eyes, or allow your cat to ingest this product. The product is bitter tasting and salivation may occur for a short time if the cat licks the product immediately after treatment.* Treatment at the base of the skull will minimize the opportunity for the cat to lick the product. Do not allow the product to run off.

[Visuals Depicting Application to Animal]

6. Discard empty tube as described in Storage and Disposal.
7. Under normal conditions this product is effective for a month. However, in case of severe flea infestation, retreatment may be necessary earlier than four (4) weeks. Do not retreat more often than once every seven (7) days. After flea control is attained, return to a monthly retreatment schedule.

PRODUCT INFORMATION

The successive feeding activity of fleas on cats frequently elicits a hypersensitivity skin disorder known as flea allergy dermatitis (FAD) or flea bite hypersensitivity. Treatment of cats with Advantage® II Small Cat kills fleas and may reduce the incidence of this condition.

Advantage® II Small Cat kills the existing fleas on cats within 12 hours. Reinfesting fleas are killed within 2 hours with protection against further flea infestation lasting for up to four (4) weeks. Pre-existing pupae in the environment may continue to emerge for six (6) weeks or longer depending upon the climatic conditions.

Fleas, eggs and larvae in the cat's surroundings are killed following contact with an Advantage® II Small Cat treated cat. Advantage® II Small Cat provides multi-stage flea control effectively breaking all flea life-cycle stages for lasting control of flea populations.

Advantage® II Small Cat kills adult fleas quickly, within 12 hours, inhibits the development of immature flea life stages and prevents them from reaching the biting adult stage.

Advantage® II Small Cat is waterproof and remains effective following a shampoo treatment or after exposure to rain or sunlight.

Apply monthly treatments for optimal control and prevention of fleas.

KEEP OUT OF REACH OF CHILDREN

CAUTION

PRECAUTIONARY STATEMENTS
HAZARDS TO HUMANS

CAUTION: Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling. Keep out of reach of children. Do not contaminate feed or food.

FIRST AID	
If Swallowed:	• Call a poison control center or doctor immediately for treatment advice. • Have person sip a glass of water if able to swallow. • Do not induce vomiting unless told to do so by the poison control center or doctor. • Do not give anything to an unconscious person.
If In Eyes:	• Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. • Call a poison control center or doctor for treatment advice.
If On Skin	• Wash with plenty of soap and water.
HOT LINE NUMBER	
Have the product container or label with you when calling a poison control center or doctor, or going for treatment. For medical emergencies call 1-800-422-9874. For customer questions call 1-800-255-6826.	
NOTE TO PHYSICIAN	
Treat the patient symptomatically.	

HAZARDS TO DOMESTIC ANIMALS

For external use only. Do not apply to cats or kittens under 8 weeks of age or weighing less than 5 lbs. As with any product, consult your veterinarian before using this product on debilitated, aged, pregnant or nursing cats. Individual sensitivities, while rare, may occur after using ANY pesticide product for cats. If signs persist, or become more severe, consult a veterinarian immediately. If your cat is on medication, consult your veterinarian before using this or any other product.

Side Effects: Monitor your cat after application. Side effects, although very rare, may include signs of skin irritation such as redness, scratching, or other signs of discomfort. Gastrointestinal signs such as hypersalivation, vomiting or diarrhea have also been reported. If these or other side effects (such as lethargy) occur, consult your veterinarian or call 1-800-422-9874.

For consumer questions call 1-800-255-6826.
For medical emergencies call 1-800-422-9874.

RESTRICTIONS:

- Use only on cats or kittens 8 weeks and older and weighing 5 – 9 lbs. Do not use on other animals.
- Do not apply more than one (1) tube per treatment.
- Do not have contact or allow children to have contact with treated area until completely dry.

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal.

Pesticide Storage: Store in a cool, dry place inaccessible to children and pets. **Pesticide Disposal and Container Handling:** Nonrefillable container. **If empty**: Do not reuse or refill this container. Place in trash or offer for recycling if available. **If partly filled**: Call your local solid waste agency or 1-800-422-9874 for disposal instructions. Never place unused product down any indoor or outdoor drain.

LIMITED WARRANTY AND LIMITATION OF DAMAGES

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For more information visit www.petparents.com

[Label on Individual Tube]

Advantage® II Small Cat

9.10% Imidacloprid

0.46% Pyriproxyfen

0.014 fl. oz. (0.4 mL)

EPA Reg. No. 11556-151

Keep Out of Reach of Children

CAUTION

Read The Entire Label Before Use

BAYER

Lot No. 0000000

[OPTION 1: Label on blister card; one card containing 1, 2, 3, 4, 5, or 6 tubes]
[OPTION 2: Label on pouch containing one tube]

[Additional label text for OPTION 2: THIS UNIT NOT FOR RETAIL SALE]

Advantage® II Small Cat

For external use only on cats and kittens 8 weeks and older and weighing 5 - 9 lbs.

9.10% Imidacloprid

0.46% Pyriproxyfen

[X] - 0.014 fl. oz. (0.4 mL) Tube(s)

EPA Reg. No. 11556-151

BAYER

NOTE TO REVIEWER: [(Brackets and parentheses indicate alternate language)]

OPTIONAL MARKETING CLAIMS [Appearing on any panel]

- For use on cats and kittens 8 weeks of age and older
- Advantage II contains [imidacloprid], [and an/the] [insect growth regulator] [IGR] [pyriproxyfen]
- A single topical application remains effective for up to [4 weeks] [a month]
- Convenient, easy-to-apply topical solution
- Convenient, easy-to-apply and fragrance free [monthly] [topical solution]
- Once a month topical flea prevention and treatment for cats 8 weeks of age or older
- Advantage II is indicated for the prevention and treatment of fleas on cats 8 weeks of age and older
- For the prevention and treatment of flea infestations
- One treatment prevents further flea infestations for up to [4 weeks] [a month]
- Kills fleas on cats within [12] hours and continues to prevent infestations for up to [four weeks] [a month]
- Kills fleas before they lay eggs
- Larval flea stages in the cat's environment are killed following contact with an Advantage II treated cat
- Kills larval stages of fleas following contact with an Advantage II treated cat
- Kills fleas within [12] hours of application
- Stops existing flea infestations by killing adult fleas
- Prevents reinfestations by killing adult fleas before they lay eggs
- Reinfesting fleas are killed within 2 hours with protection against further flea infestation
- [Prevents] [Stops] flea eggs from hatching [into biting adults]
- Effectively breaks the flea life cycle
- [Kills] [Controls] all flea life stages
- Comprehensive flea prevention and treatment
- 3-way flea protection ([kills] [controls]) adults, larvae, and eggs
- [Prevents] [Stops] flea eggs from developing into [(biting) (adult)] fleas
- Treatment with Advantage II kills fleas and may reduce the incidence of flea allergic dermatitis [FAD] or flea bite hypersensitivity
- Flea adulticide, larvicide, and ovicide
- Kills flea eggs
- Controls flea problems
- Provides flea protection
- Controls existing fleas and flea eggs plus [and] [prevents] future flea infestations
- Advantage II may be used year-round for flea [prevention][protection]

- Contains an insect growth regulator (IGR) to kill flea eggs and prevent re-infestation
- Monthly use of Advantage II kills fleas and may prevent ([flea allergy dermatitis][flea bite hypersensitivity])
- Controls existing flea infestations on your cat and prevents further infestations
- Prevents fleas on treated cats from infesting (reinfesting)
- Remains effective after bathing
- Remains effective following shampooing
- Waterproof
- Remains effective after exposure to rain or sunlight
- Fragrance-free
- In child-resistant packaging
- Starts working through contact

DATA PACKAGE BEAN SHEET

Date: 15-Jan-2013

Decision #: 473349
DP #: (406179)
PRIA
Parent DP #:
Submission #: 928410
E-Sub #:

* * * Registration Information * * *

Registration: 11556-151 - ADVANTAGE II SMALL CAT

Company: 11556 - BAYER HEALTHCARE LLC

Risk Manager: RM 01 - Venus Eagle - (703) 308-8045 Room# PY1 S-7913

Risk Manager Reviewer: Jennifer Urbanski JURBANSK

Sent Date: _____ PRIA Due Date: 09-May-2013 Edited Due Date: _____

Type of Registration: Product Registration - Section 3

Action Desc: (R340) AMENDMENT;NON-FAST TRACK;REVIEW WITHIN RD, E.G. PRECAUTIONARY LAE

Ingredients: 129032, Pyriproxyfen(.46%)

129099, Imidacloprid(9.1%)

* * * Data Package Information * * *

Expedite: ◯ Yes ● No Date Sent: 10-Jan-2013 Due Back: _____

DP Ingredient: 129032, Pyriproxyfen

129099, Imidacloprid

DP Title: _____

CSF Included: ● Yes ◯ No Label Included: ● Yes ◯ No Parent DP #: _____

Assigned To		Date In	Date Out		
Organization:	RD / TRB	15-Jan-2013	3/19/13	Last Possible Science Due Date:	09-Apr-2013
Team Name:	Child Resistant Packaging	15-Jan-2013		Science Due Date:	
Reviewer Name:				Sub Data Package Due Date:	
Contractor Name:					

* * * Studies Sent for Review * * *

No Studies

* * * Additional Data Package for this Decision * * *

No Additional Data Packages

* * * Data Package Instructions * * *

Please review the data submitted under 11556-128 to determine if the new child resistant packaging for this product is acceptable. The registrant indicated that the packaging for the two products is exactly the same. Attached is the summary, the label and the CSF. The data matrix and the cover letter are the same as for 11556-152 and can be found in that package.

Feel free to contact the company directly if need be.

Thanks!

Use 11556-128

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

CHILD-RESISTANT PACKAGING REVIEW
Technical Review Branch

IN 01/15/2013 & 03/13/2013 OUT 03/19/2013

RD, TRB, Reviewed by Rosalind L. Gross 03/19/2013

EPA Reg. No. or File Symbol 11556-125, 127, 128, 130, 150, 151 (uses11556-128 data), and 152

DP Barcode DP408182, 408183, 408184, 408185, 409881, 408181, 408179, 408177,

Decision # 473346, 473347, 473348, 473309, 473308, 473349, 473345,
EPA Petition or EUP No. _____

Date Division Received 12/19/2012

Type Product(s) Insecticide (flea product)

Data Accession No(s). MRID numbers 49023701 (GLM12443), 49023702 (GLM12443), 49022901 (GLM12442), 49022902 (GLM12442), 49023601 (GLM12445), 49023602 (GLM12445), 49022801 (GLM12441), 49022802 (GLM12441), 49022803 (GLM12447), 49022804 (GLM12447), 49060301 (GLM13047), 49060302 (GLM13047), 49060303 (GLM13049), 49060304 (GLM13049), 49023801 (GLM12446), 49023802 (GLM12446), 49023901 (GLM12444), and 49023902 (GLM12444)

Product Mgr./Chemical Review Mgr/Contact Person RM 01 Jennifer Urbanski
Division RD

Product Name(s) Advantage II Medium Dog, Advantage II Large Dog, Advantage II Small Dog, Advantage II Extra Large Dog, Advantage II Kitten, Advantage II Small Cat, and Advantage II Large Cat

Company Name(s) Bayer Healthcare LLC

Submission Purpose: Review of CRP studies to determine if they are adequate to support CRP certification for this product in 5 fill levels in a thin film pouch and 1 fill level in a thick film pouch in 2 sizes (4 or 6 pouches/ package)

Active Ingredient(s), PC code, & %: Imidacloprid 9.1%
Pyriproxyfen 0.46%

Summary of Findings

The Agency concludes all the requirements for CRP are met for EPA Registration Number 11556-125, 127, 128, 130, 150, 151, and 152 based on the more stringent definition of a senior failure in combination with the Senior Adult Use Effectiveness (SAUE) being 96% or more with the one exception noted (see conclusion for details). For the details of each study refer to the attached summary chart (selfcertreviewsummarychtbayer2013.doc).

The **CRP certifications submitted December 12, 2012** (EPA Registration Number 11556-125, 127, 128, 150, 151, and 152) and **February 14, 2013** (EPA Registration Number 11556-130) **are acceptable. The December 12, 2012 labels** for EPA Registration Number 11556-125, 127, 128, 130, 150, 151, and 152 have the CRP directions used in SAUE testing. **The directions on opening the package given to consumers must be identical to those given to the seniors during testing for the pouches (see package section for exact language).** Note EPA Registration Number 11556-127 (GLM12442) the fluid ounces on the label for the tube and pouch should read 0.085 fluid ounces.

Should any human experience/epidemiological evidence indicate a problem once the product is in the marketplace, the Agency reserves the right to reexamine this data comprehensively and to question the child resistance of the package involved.

Package

The package consists of a pouch, which is the child-resistant feature, containing a white plastic tube with a white closure. The tube is opened by removing the closure, inverting it and twisting it to break the seal on the tube. Then the closure is removed and the product is dispensed. The pouch looks like:

The pouch is either a thin film PET/AL/PE 12/12/40 pouch or a thick film PET/AL/PE 23/12/50 pouch dependent on the fill size. The thin film PET/AL/PE 12/12/40 pouch is used for the 1ml, 2.5ml, 0.4ml, 0.23ml, and 0.8ml fill levels (EPA Registration Number 11556-125, 127, 128, 150, 151, and 152). The thick film PET/AL/PE 23/12/50 pouch is used for the 4ml fill level (EPA Registration Number 11556-130). The thin and thick film pouches will be in sizes of 4 or 6 pouches per package. The pouch has no instructions for opening on it. The instructions given to seniors during CRP testing were on a label given to them along with a pair of scissors. The instructions on the label said:

HOW TO OPEN

- Be sure tube is at bottom of pouch.
- Using scissors, cut the pouch across the top and remove tube.

Toxicity

The toxicity of the product, which contains 9.1% Imidacloprid and 0.46% Pyriproxyfen, is based on toxicity data for a 9.0% Imidacloprid and 0.48% Pyriproxyfen formulation. The acute oral LD_{50} study MRID 47089411 (9.0% Imidacloprid and 0.48% Pyriproxyfen) is 1098mg/kg for the female rat, no male rat was used in the study. The toxic or harmful amount for an 11.4 kg child is 12.5g (1098mg/kg x 11.4kg), which is 11.4ml of product (12.5g divided by 1.092g/ml [product density]).

Failure

For the purposes of CRP testing **a child failure** is access to 12.5g = 11.4ml or 9 pouches, whichever is less. The number of pouches is a function of the number of ml per pouch. In **no case is access to one pouch a child failure.** For the number of pouches for each product see the table below:

EPA REG #	Product Density mg/ml	Pkg Size	fill level amt ml (ml = 0.0338 fl. oz.)	fill level fl. oz.	# units = toxic amt	# units = child failure
11556-125	1092	4 or 6 pouches	1ml	0.0338 = 0.034	11.4 = 12	9
11556-127	1092	4 or 6 pouches	2.5ml	0.0845 = 0.085	4.56 = 5	5
11556-128	1092	4 or 6 pouches	0.4ml	0.01352 = 0.014	28.5 = 29	9
11556-130	1092	4 or 6 pouches	4ml	0.1352 = 0.135	2.85 = 3	3
11556-150	1092	4 or 6 pouches	0.23ml	0.007774 = 0.0078	49.56 = 50	9
11556-151 (use 11556-128)	1092	4 or 6 pouches	0.4ml	0.01352 = 0.014	28.5 = 29	9

EPA REG #	Product Density mg/ml	Pkg Size	fill level amt ml (ml = 0.0338 fl. oz.)	fill level fl. oz.	# units = toxic amt	# units = child failure
11556-152	1092	4 or 6 pouches	0.8ml	0.02704 = 0.027	14.25 = 15	9

A **pouch failure** is any opening or leakage of the pouch.
A **Senior Adult Use Effectiveness (SAUE) failure** is failure to open a pouch, tube, or pouch and tube in the 5 minute test period, or failure to open a pouch, tube, or pouch and tube in the 1 minute test period.

Analysis of Data

The CRP summaries of the test data, which agreed with the complete review for the studies, were included. A computer analysis and complete review of the 9 Child-Resistant Effectiveness (CRE) and 9 SAUE studies were not done. We used the summaries of the test data[1], a computer analysis of the worst case study and a computer analysis for the thick film pouch that underwent SAUE testing in strict accordance with 16 CFR 1700.20 were done. This means a computer analysis was done for the 4 ml thin film pouch (PET/AL/PE 12/12/40) with the lowest SAUE including the lowest CRE (MRID 49022802 (GLM12441) and 49022801 (GLM12441)) and a computer analysis was done for the 4 ml thick film pouch (PET/AL/PE 23/12/50) as a 6 pouch package (MRID 49060304 (GLM13049) and MRID 49060303 (GLM13049)). The results of our review are:

Child Study 4ml thin film pouch (PET/AL/PE 12/12/40) (lowest CRE MRID49022801 (GLM12441)) involved giving each child 4 pouches each containing 4ml of water at the start of the test. A child failure was defined as access to 3 pouches as the pouch was the child-resistant feature. The results from computer analysis were a 50 child test had 5 failures. The failures were 5 children accessing 3 pouches each. There were also 4 children who accessed 2 pouches and 11 children who accessed 1 pouch. A total 20 children accessed 1 or more pouches each. The CRP summary of the test data agreed with these results. **This study was a pass according to the child sequential test** in

1 Since the CRP summaries agreed with the complete review for the studies, they were used instead of the complete review.

16 CFR 1700.20.

Senior Adult Use Effectiveness Study 4ml thin film pouch (PET/AL/PE 12/12/40) (lowest SAUE MRID49022802 (GLM12441)) involved having the test subjects open one pouch during a 5 minute test period and one pouch during a one minute test period. Scissors were made available during testing because the test directions given to the seniors called for their use. The results from computer analysis were 95% SAUE with 5 failures to open the pouch in the 1 minute test period. **The CRP summary of the test data did not agree with these results.** The registrant defined a failure more **stringently.**[2] Based on the aforementioned more stringent definition of a failure the CRP summary results were 92% SAUE with the senior receiving one pouch for the 5 minute and 1 minute test period. The 8 failures were 5 seniors failed to open the tube during the 5 minute test period, 3 seniors failed to open the pouch and tube during the 1 minute test period. **SAUE testing was not done in strict accordance with 16 CFR 1700.20.**[3] **The study is a pass of the Senior Adult test in 16 CFR 1700.20 and the effectiveness specifications in 16 CFR 1700.15(b).**

Child Study 4ml thick film pouch (PET/AL/PE 23/12/50) as a 6 pouch package (MRID 49060303 (GLM13049)) involved giving each child 6 pouches each containing 4ml of water at the start of the test. A child failure was defined as access to 3 pouches as the pouch was the child-resistant feature. The results from computer analysis were a 50 child test had 2 failures. The failures were 2 children accessing 3 pouches each. There were also 2 children who accessed 2 pouches and 4 children who accessed 1 pouch. A total 8 children accessed 1 or more pouches each. The CRP summary of the test data agreed with these results. **This study was a pass according to the child sequential test in 16 CFR 1700.20.**

Senior Adult Use Effectiveness Study 4ml thick film pouch (PET/AL/PE 23/12/50) as a 6 pouch package (MRID 49060304 (GLM13049)) involved giving the seniors 6 pouches at the beginning of each test period and having the test subjects open one pouch during a 5 minute test period and one pouch during a one minute test period. Scissors were made available during testing because the test directions given to the seniors called for their use. The results from computer analysis were 99% SAUE with 1 failure to open the pouch in the 1 minute test period. **The CRP summary of the test data did not agree with these results.** The registrant defined a failure more **stringently.**[4] Based on the aforementioned more stringent definition of a failure the

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2 A failure was defined as a failure to open a pouch, tube, or pouch and tube in the 5 minute test period, or failure to open a pouch, tube, or pouch and tube in the 1 minute test period.

3 The senior received one pouch not the 4 or 6 pouches in a package at the start of the 5 minute and 1 minute test period.

4 A failure was defined as a failure to open a pouch, tube, or pouch and tube in the 5

CRP summary results were 96% SAUE. The 4 failures were 1 senior failed to open the tube during the 5 minute test period, 3 seniors failed to open the pouch and tube during the 1 minute test period. **SAUE testing was done in strict accordance with 16 CFR 1700.20. The study is a pass of the Senior Adult test in 16 CFR 1700.20 and the effectiveness specifications in 16 CFR 1700.15(b).**

For the details of each study refer to the attached summary chart (selfcertreviewsummarychtbayer2013.doc).

Conclusion

Review of CRP summaries of the test data and the computer analysis of the data revealed that only 2 of the 9 SAUE studies were done in strict accordance with 16 CFR 1700.20 (EPA Registration Number 11556-130 4ml 6 pack (MRID 49060302 (GLM 13047) and MRID 49060304 (GLM13049)). However, the use of the other 7 SAUE studies where the seniors only received one pouch at the beginning of the 5 minute test period and the **1 minute** test period **will be allowed based on the results for the SAUE all being 96% or above.** The **one exception is for the 4ml thin film pouch (PET/AL/PE 12/12/40), which will not be used** as either a 4 pouch or 6 pouch package per the February 14, 2013 CRP certification for EPA Registration Number 11556-130.

Furthermore, the discrepancies in the SAUE between the CRP summaries and the computer analysis were based on the registrant defining a failure more stringently than the regulations in 16 CFR 1700.20. **The Agency will accept and use the more stringent definition of a senior failure specified by the registrant (and noted herein).**

The Agency concludes all the requirements for CRP are met for EPA Registration Number 11556-125, 127, 128, 130, 150, 151, and 152 based on the more stringent definition of a senior failure in combination with the SAUE being 96% or more with the one exception noted above. For the details of each study refer to the attached summary chart (selfcertreviewsummarychtbayer2013.doc).

The **CRP certifications submitted December 12, 2012** (EPA Registration Number 11556-125, 127, 128, 150, 151, and 152) and **February 14, 2013** (EPA Registration Number 11556-130) **are acceptable. The December 12, 2012 labels** for EPA Registration Number **11556-125, 127, 128, 130, 150, 151, and 152** have the CRP directions used in SAUE testing. **The CRP directions in all locations on the final stamped label must be identical to those used in SAUE testing (see package section for exact language).** Note EPA Registration Number 11556-127

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minute test period, or failure to open a pouch, tube, or pouch and tube in the 1 minute test period.

(GLM12442) the fluid ounces on the label for the tube and pouch should read 0.085 fluid ounces.

Should any human experience/epidemiological evidence indicate a problem once the product is in the marketplace, the Agency reserves the right to reexamine this data comprehensively and to question the child resistance of the package involved.

CRPdatasummarycht
Self Cert Summary Data **March 15, 2013**

Company Name - Bayer 11556

Chemical - Imidacloprid 9.1% & Pyriproxyfen 0.46%

Access to a toxic or harmful amt = acute oral LD_{50} 1098mg/kg female rat MRID 47089411 (July 2007) multiplied by 11.4kg = **12.5g**
Access to a toxic or harmful amt = 12.5g divided by 1.092g/ml (product density) = **11.4ml**
pouch thin = PET/AL/PE 12/12/40
pouch thick = PET/AL/PE 23/12/50
pouch is marketed as 4 pouch or 6 pouch package

A **Senior Adult Use Effectiveness failure** is failure to open: Package A pouch in the 5 minute test period, Package A tube in the 5 minute test period, Package A pouch and tube in the 5 minute test period, Package B pouch in the 1 minute test period, Package B tube in the 1 minute test period, or Package B pouch and tube in the 1 minute test period.
A **child failure** is access to 12.5g, which is equal to **11.4ml**. The number of units is a function of the number of ml per unit.
A **unit failure** is any opening or leakage of the pouch.

*** SAS value differs from GLM Summary and Report**
For child test values new corrected SAS files were submitted and reviewed.
For senior test values the discrepancy is due to more stringent definition of senior failure to include failure to access to pouch (CR feature) and/or to access tube. [Access to the tube is not part of the senior definition of failure per 16 CFR 1700.20. Resecuring for a unit package (package A or package B) is not part of the senior definition of failure per 16 CFR 1700.20.] The results are coded by GLM such that a failure to open a tube is considered a resecuring failure for the package involved. SAS interprets a failure to resecure package A (not opening the tube per GLM) as a failure to open package B. SAS interprets a failure to resecure package B (not opening the tube per GLM) as an unrecorded incident, which is why the SAS SAUE is higher than the GLM reported SAUE. For the purposes of the review of these data the GLM reported SAUE values will be used.

Self Cert Summary Data

EPA REG #	MRID	PKG Description fill size ml, size unit ml, # unit/pkg, color, (ml = 0.0338 fl. oz.)	# units = child failure	# Pkges Child Get at Begin Test	CRE # child test	SAUE % #pkg to senior	Conclusion include CRE & SAUE via computer analysis (SAS)
11556-125 GLM12443	49023701 38989 child 49023702 38990 senior	1ml thin	9	10	50 child 1 F	98 1 Pouch	**CRP Cert** date & status 12/12/2012 acceptable **Label** dated 12/12/2012 acceptable uses the same CRP directions as in SAUE study **Label is limited to SAUE test pkg instruct.** **Meet 16 CFR 1700.20 CRE Criteria - yes** **Meet 16 CFR 1700.20 SAUE Criteria - yes** The study is a pass of the child test according to the sequential test chart in 16 CFR 1700.20. The study is a pass of the senior adult test in 16 CFR 1700.20 and the effectiveness specifications in 16 CFR 1700.15(b). all requirements for CRP per 16 CFR 1700.20 - **yes**
11556-127 GLM12442	49022901 38987 child 49022902 38988 senior	2.5ml thin	5	6	50 child 0 F	100 1 Pouch	**CRP Cert** date & status 12/12/2012 acceptable **Label** dated 12/12/2012 acceptable uses the same CRP directions as in SAUE study **Label is limited to SAUE test pkg instruct.** Note fl. oz. on label for tube and pouch should read 0.085 fl. oz. **Meet 16 CFR 1700.20 CRE Criteria - yes** **Meet 16 CFR 1700.20 SAUE Criteria - yes** The study is a pass of the child test according to the sequential test chart in 16 CFR 1700.20. The study is a pass of the senior adult test in 16 CFR 1700.20 and the effectiveness specifications in 16 CFR 1700.15(b). all requirements for CRP per 16 CFR 1700.20 - **yes**

EPA REG #	MRID	PKG Description fill size ml, size unit ml, # unit/pkg, color, (ml = 0.0338 fl. oz.)	# units = child failure	# Pkges Child Get at Begin Test	CRE # child test	SAUE % #pkg to senior	Conclusion include CRE & SAUE via computer analysis (SAS)
11556-128 GLM12445	49023601 38993 child 49023602 38994 senior	0.4ml thin	9	10	50 child 0 F	98 1 Pouch	**CRP Cert** date & status 12/12/2012 acceptable **Label** dated 12/12/2012 acceptable uses the same CRP directions as in SAUE study **Label is limited to SAUE test pkg instruct.** **Meet 16 CFR 1700.20 CRE Criteria - yes** **Meet 16 CFR 1700.20 SAUE Criteria - yes** The study is a pass of the child test according to the sequential test chart in 16 CFR 1700.20. The study is a pass of the senior adult test in 16 CFR 1700.20 and the effectiveness specifications in 16 CFR 1700.15(b). all requirements for CRP per 16 CFR 1700.20 - **yes**
11556-130 GLM12441	49022801 38985 child 49022802 38986 senior	4ml thin 4 pack	3	4	50 child 5 F	92 1 Pouch 5F open pkg A tube, 3F open pkg B pouch & tube in 60 sec	**CRP Cert** date & status 2/14/2013 acceptable **Label** dated 12/12/2012 acceptable uses the same CRP directions as in SAUE study **Label is limited to SAUE test pkg instruct.** **CRE** * results from computer analysis 50 child 5 F - 5 children access 3 units, 4 children access 2 units, 11 children access 1 unit. 20 children access 1 or more units. **SAUE** * results from computer analysis 95% SAUE 5 F pkg B **Meet 16 CFR 1700.20 CRE Criteria - yes** **Meet 16 CFR 1700.20 SAUE Criteria - yes** The study is a pass of the child test according to the sequential test chart in 16 CFR 1700.20. The study is a pass of the senior adult test in 16 CFR 1700.20 and the effectiveness specifications in 16 CFR 1700.15(b). all requirements for CRP per 16 CFR 1700.20 - **yes**

EPA REG #	MRID	PKG Description fill size ml, size unit ml, # unit/pkg, color, (ml = 0.0338 fl. oz.)	# units = child failure	# Pkges Child Get at Begin Test	CRE # child test	SAUE % #pkg to senior	Conclusion Include CRE & SAUE via computer analysis (SAS)
11556-130 GLM 12447	49022803 38997 child 49022804 38998 senior	4ml thick 4 pack	3	4	50 child 2 F	96 1 Pouch	**CRP Cert** date & status 2/14/2013 acceptable **Label** dated 12/12/2012 acceptable uses the same CRP directions as in SAUE study **Label is limited to SAUE test pkg instruct.** **CRE** " results from computer analysis 50 child 2 F - 2children access 3 units, 5 children access 1 unit. 7 children access 1 or more units. **Meet 16 CFR 1700.20 CRE Criteria -yes** **Meet 16 CFR 1700.20 SAUE Criteria -yes** The study is a pass of the child test according to the sequential test chart in 16 CFR 1700.20. The study is a pass of the senior adult test in 16 CFR 1700.20 and the effectiveness specifications in 16 CFR 1700.15(b). all requirements for CRP per 16 CFR 1700.20 - yes
11556-130 GLM13047	49060301 39265 child 49060302 39266 senior	4ml thin 6pack	3	6	50 child 5 F	93 6 Pouch	**CRP Cert** date & status 2/14/2013 acceptable **Label** dated 12/12/2012 acceptable uses the same CRP directions as in SAUE study **Label is limited to SAUE test pkg instruct.** **Meet 16 CFR 1700.20 CRE Criteria - yes** **Meet 16 CFR 1700.20 SAUE Criteria - yes** The study is a pass of the child test according to the sequential test chart in 16 CFR 1700.20. The study is a pass of the senior adult test in 16 CFR 1700.20 and the effectiveness specifications in 16 CFR 1700.15(b). all requirements for CRP per 16 CFR 1700.20 - yes

EPA REG #	MRID	PKG Description fill size ml, size unit ml, # unit/pkg, color, (ml = 0.0338 fl. oz.)	# units = child failure	# Pkges Child Get at Begin Test	CRE # child test	SAUE % #pkg to senior	Conclusion include CRE & SAUE via computer analysis (SAS)
11556-130 GLM13049	49060303 39267 child 49060304 39268 senior	4ml thick 6pack	3	6	50 child 2 F	96 6 Pouch 1F open pkg A tube, 3F open pkg B pouch & tube in 60 sec	**CRP Cert** date & status 2/14/2013 acceptable **Label** dated 12/12/2012 acceptable uses the same CRP directions as in SAUE study **Label is limited to SAUE test pkg instruct.** **CRE** results from computer analysis 50 child 2 F - 2 children access 3 units, 2 children access 2 units, 4 children access 1 unit. 8 children access 1 or more units. **SAUE** * results from computer analysis 99% SAUE 1 F pkg B **Meet 16 CFR 1700.20 CRE Criteria - yes** **Meet 16 CFR 1700.20 SAUE Criteria - yes** The study is a pass of the child test according to the sequential test chart in 16 CFR 1700.20. The study is a pass of the senior adult test in 16 CFR 1700.20 and the effectiveness specifications in 16 CFR 1700.15(b). all requirements for CRP per 16 CFR 1700.20 - yes
11556-150 GLM12446	49023801 38995 child 49023802 38996 senior	0.23ml thin	9	10	50 child 0 F	96 1 Pouch	**CRP Cert** date & status 12/12/2012 acceptable **Label** dated 12/12/2012 acceptable uses the same CRP directions as in SAUE study **Label is limited to SAUE test pkg instruct.** **Meet 16 CFR 1700.20 CRE Criteria - yes** **Meet 16 CFR 1700.20 SAUE Criteria - yes** The study is a pass of the child test according to the sequential test chart in 16 CFR 1700.20. The study is a pass of the senior adult test in 16 CFR 1700.20 and the effectiveness specifications in 16 CFR 1700.15(b). all requirements for CRP per 16 CFR 1700.20 - yes

EPA REG #	MRID	PKG Description fill size ml, size unit ml, # unit/pkg, color, (ml = 0.0338 fl. oz.)	# units = child failure	# Pkges Child Get at Begin Test	CRE # child test	SAUE % #pkg to senior	Conclusion Include CRE & SAUE via computer analysis (SAS)
11556-151 (use 11556-128) GLM12445	49023601 38993 child 49023602 38994 senior	0.4ml thin	9	10	50 child 0 F	98 1 Pouch	**CRP Cert** date & status 12/12/2012 acceptable **Label** dated 12/12/2012 acceptable uses the same CRP directions as in SAUE study **Label is limited to SAUE test pkg instruct.** **Meet 16 CFR 1700.20 CRE Criteria - yes** **Meet 16 CFR 1700.20 SAUE Criteria - yes** The study is a pass of the child test according to the sequential test chart in 16 CFR 1700.20. The study is a pass of the senior adult test in 16 CFR 1700.20 and the effectiveness specifications in 16 CFR 1700.15(b). all requirements for CRP per 16 CFR 1700.20 - yes
11556-152 GLM12444	49023901 38991 child 49023902 38992 senior	0.8ml thin	9	10	50 child 3 F	96 1 Pouch	**CRP Cert** date & status 12/12/2012 acceptable **Label** dated 12/12/2012 acceptable uses the same CRP directions as in SAUE study **Label is limited to SAUE test pkg instruct.** **Meet 16 CFR 1700.20 CRE Criteria - yes** **Meet 16 CFR 1700.20 SAUE Criteria - yes** The study is a pass of the child test according to the sequential test chart in 16 CFR 1700.20. The study is a pass of the senior adult test in 16 CFR 1700.20 and the effectiveness specifications in 16 CFR 1700.15(b). all requirements for CRP per 16 CFR 1700.20 - yes

Please read instructions on reverse before completing form. Form Approved, OMB No. 2070-0060

EPA

United States
Environmental Protection Agency
Washington, DC 20460

☐ **Registration**
☒ **Amendment**
☐ **Other:**

OPP Identifier Number

Application for Pesticide - Section I

1. Company/Product Number	2. EPA Product Manager	3. Proposed Classification
11556-151	V. Eagle	☒ None ☐ Restricted
4. Company/Product (Name)	PM#	
Advantage II Small Cat	01	

5. Name and Address of Applicant *(Include ZIP Code)*
Bayer HealthCare LLC, Animal Health Division
PO Box 390
Shawnee Mission, KS 66201

☐ *Check if this is a new address*

6. **Expedited Review.** In accordance with FIFRA Section 3(c)(3)(b)(I), my product is similar or identical in composition and labeling to:
EPA Reg. No. _____
Product Name _____

Section - II

☒ Amendment – Explain below.
☐ Resubmission in response to Agency letter dated _____
☐ Notification - Explain below.
☐ Final printed labels in response to Agency letter dated _____
☐ "Me Too" Application
☐ Other - Explain below

Explanation: [R340] - Amendment requiring data review within RD (new Child-Resistant Packaging) with respective changes in package opening instructions. See attachment for details.

Section - III

1. Material This Product Will Be Packaged In:

Child-Resistant Packaging	Unit Packaging	Water Soluble Packaging	2. Type of Container
☒ Yes*	☐ Yes	☐ Yes	☐ Metal
☐ No	☒ No	☒ No	☒ Plastic Tube
	If "Yes" Unit Packaging wgt. / No. per container	If "Yes" Package wgt. / No. per container	☐ Glass
***Certification must be submitted**			☒ Paper
			☒ Other (Specify) Foil

3. Location of Net Contents Information	4. Size(s) Retail Container	5. Location of Label Directions
☒ Label ☐ Container	0.4 mL Tube / 4 or 6 per box	☐ On Label ☒ On labeling accompanying product

6. Manner in Which Label is Affixed to Product
☒ Lithograph ☐ Paper glued ☐ Stenciled ☐ Other _____

Section - IV

1. Contact Point *(Complete items directly below for identification of individual to be contacted, if necessary, to process this application)*

Name	Title	Telephone No. (Include Area Code)
Douglas A. Spilker, Ph.D.	Manager, EPA Reg. Affairs	913-268-2751

Certification

I certify that the statements I have made on this form and all attachments thereto are true, accurate and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine or imprisonment or both under applicable law.

6. Date Application Received **(Stamped)**

2. Signature	3. Title
Douglas A. Spilker	Manager, EPA Reg. Affairs
4. Typed Name	5. Date
Douglas A. Spilker (doug.spilker@bayer.com)	14 Dec 2012

EPA Form 8570-1 (Rev. 8-94) Previous editions are obsolete — White- EPA File Copy (original) Yellow- Applicant Copy

Form Approved OMB Nos. 2070-0060; 2070-0057; 2070-0107; 2070-0122; 2070-0154

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
1200 Pennsylvania Avenue, N.W.
WASHINGTON, D.C. 20460

Paperwork Reduction Act Notice: The public reporting burden for this collection of information is estimated to average 1.25 hours per response for registration and 0.25 hours per response for reregistration and special review activities, including time for reading the instructions and completing the necessary forms. Send comments regarding burden estimate or any other aspect of this collection of information, including suggestions for reducing the burden to: Director, Collection Strategies Division (2822T), U.S. Environmental Protection Agency, 1200 Pennsylvania Avenue, N.W., Washington, DC 20460. Do not send the completed form to this address.

Certification with Respect to Citation of Data

Applicant's/Registrant's Name, Address, and Telephone Number	EPA Registration Number/File Symbol
Bayer HealthCare LLC, Animal Health Div., POB 390, Shawnee Mission KS 66201 (913-268-2751)	11556-115
Active Ingredient(s) and/or representative test compound(s) Imidacloprid + Pyriproxyfen	Date December 14, 2012
General Use Pattern(s) (list all those claimed for this product using 40 CFR Part 158) Indoor; Non-food Use	Product Name Advantage II Small Cat

NOTE: If your product is a 100% repackaging of another purchased EPA-registered product labeled for all the same uses on your label, you do not need to submit this form. You must submit the Formulator's Exemption Statement (EPA Form 8570-27).

☐ I am responding to a Data-Call-In Notice, and have included with this form a list of companies sent offers of compensation (the Data Matrix form should be used for this purpose).

SECTION I: METHOD OF DATA SUPPORT (Check one method only)

☐ I am using the cite-all method of support, and have included with this form a list of companies sent offers of compensation (the Data Matrix form should be used for this purpose).	☑ I am using the selective method of support (or cite-all option under the selective method), and have included with this form a completed list of data requirements (the Data Matrix form must be used).

SECTION II: GENERAL OFFER TO PAY

(Required if using the cite-all method or when using the cite-all option under the selective method to satisfy one or more data requirements)

☑ I hereby offer and agree to pay compensation, to other persons, with regard to the approval of this application, to the extent required by FIFRA.

SECTION III: CERTIFICATION

I certify that this application for registration, this form for reregistration, or this Data-Call-In response is supported by all data submitted or cited in the application for registration, the form for reregistration, or the Data-Call-In response. In addition, if the cite-all option or cite-all option under the selective method is indicated in Section I, this application is supported by all data in the Agency's files that (1) concern the properties or effects of this product or an identical or substantially similar product, or one or more of the ingredients in this product; and (2) is a type of data that would be required to be submitted under the data requirements in effect on the date of approval of this application if the application sought the initial registration of a product of identical or similar composition and uses.

I certify that for each exclusive use study cited in support of this registration or reregistration, that I am the original data submitter or that I have obtained the written permission of the original data submitter to cite that study.

I certify that for each study cited in support of this registration or reregistration that is not an exclusive use study, either: (a) I am the original data submitter; (b) I have obtained the permission of the original data submitter to use the study in support of this application; (c) all periods of eligibility for compensation have expired for the study; (d) the study is in the public literature; or (e) I have notified in writing the company that submitted the study and have offered (i) to pay compensation to the extent required by sections 3(c)(1)(F) and/or 3(c)(2)(B) of FIFRA; and (ii) to commence negotiations to determine the amount and terms of compensation, if any, to be paid for the use of the study.

I certify that in all instances where an offer of compensation is required, copies of all offers to pay compensation and evidence of their delivery in accordance with sections 3(c)(1)(F) and/or 3(c)(2)(B) of FIFRA are available and will be submitted to the Agency upon request. Should I fail to produce such evidence to the Agency upon request, I understand that the Agency may initiate action to deny, cancel or suspend the registration of my product in conformity with FIFRA.

I certify that the statements I have made on this form and all attachments to it are true, accurate, and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine or imprisonment or both under applicable law.

Signature	Date	Typed or Printed Name and Title
	3-28-13	Douglas A. Spilker, Manager- EPA Reg. Affairs

EPA Form 8570-34 (12-2003) Electronic and Paper versions available. Submit only Paper version.

Bayer HealthCare
Animal Health

Via Federal Express

December 14, 2012

Document Processing Desk (REGFEE)
Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Bayer HealthCare LLC
Animal Health
P.O. Box 390
Shawnee Mission, KS 66201-0390

Attention: Ms. Venus Eagle
Registration Division

Subject: Applications for Amendment of the Registrations of:
Advantage II Kitten (EPA Reg No. 11556-150)
Advantage II Small Cat (EPA Reg. No. 11556-151)
Advantage II Large Cat (EPA Reg. No. 11556-152)
New Child-resistant packaging review (R340)

Dear Ms. Eagle:

Enclosed with this cover letter are applications for amendment of the registration of the subject three (3) companion animal (cat) spot-on products, as well as all the appropriate supporting documents and data. The purpose of this cover letter is to provide an explanatory overview of the submission which may aid in the processing of the enclosed information and respective registration applications.

Purpose of Registration Action: Bayer HealthCare, Animal Health Division, is proposing to use new child-resistant packaging for the three *Advantage II* cat products. Associated with the new CRP, new opening instructions have been added to the enclosed proposed draft labeling, text dated 12/12/12. The appropriate child resistant packaging studies are enclosed for Agency review.

Child Resistant Packaging Testing: As the Agency's files will show, because the acute oral toxicity value for the product formulation is below the 1500 mg/kg "trigger," and because this is a residential use, the products must be marketed in Child-Resistant Packaging (CRP). We currently have acceptable CRP packaging (designated as OPTION 1) data on file with the Agency (and the respective CRP Certification letters), but it is our desire to replace the current packaging with a different CRP packaging material (designated as OPTION 2). To do so, we also needed to revise the opening instructions. These new opening instructions were used in the enclosed CRP testing studies.

With regard to the overall CRP testing of the various packaging configurations, Bayer is aware of PR Notice 97-9 regarding the electronic submission of CRP test data, and therefore these data have been prepared appropriately and are included on CDs. CRP certification letters are also enclosed.

Packaging: Based on earlier CRP testing, the individual tubes alone did not qualify as child-resistant, and therefore were sold in child-resistant blisters. The current packaging for the products (designated as OPTION 1) has an outer cardboard carton with the tubes in a child-resistant blister. Instead of marketing the tubes in a blister pack, Bayer Animal Health would like the option (designated as OPTION 2) to market the product in a sealed "treasure chest" outer box containing a certain number (4 or 6) of single pouches (a single tube enclosed in a child-resistant pouch). The single pouches are made from aluminum foil [material# 01446067; PET/AL/PE 12/12/40] for the existing tubes.

The single-tube pouches will be packaged in one of two sizes of "treasure chest" outer boxes (4-tube pack/box dimension 108 x 34 x 120 mm or 6-tube pack/ box dimension 108 x 34 168 mm). However, the component of the single pouches, the aluminum pouch (and not the tube or box), is designed to be child resistant. **Please note that there are no studies submitted for the Advantage II Small Cat (11556-151) product, since the tube size (0.4 ml) is identical to that of the Advantage II Small Dog product (11556-128); the respective studies to support this tube size are being submitted concurrently with this application with the dog submission.**

Label Modifications: The enclosed draft labeling, date of draft 12/12/12, has been revised from previous draft labeling versions to add the new opening instructions (OPTION 2) – see especially highlighted draft label. See Amendment attachments for detailed information. No additional data are enclosed beyond those required for CRP certification.

We would also like to bring to your attention that concurrently with this submission, there is a submission for use of the new CRP with the four *Advantage II* dog products (11556-125, -127, -128, -130). We hope this overview cover letter is helpful in processing the attached applications. If you have any questions, please do not hesitate to call me at (913) 268-2751.

Sincerely,

Douglas A. Spilker. Ph. D.
Manager, EPA Regulatory Affairs
Doug.Spilker@Bayer.com

Enclosures

Document Processing Desk (REGFEE)
Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Enclosures:

Advantage II Kitten (11556-150)

- 1 copy proof of PRIA payment
- 1 copy Advantage II Kitten Application for Pesticide Registration with Application Attachment and two Appendices:
  Appendix 1 – CRP Data Review for Certification (Child Panel) – ID 38995
  Appendix 2 – CRP Data Review for Certification (Adult Panel) – ID 38996
- 3 copies draft labels, date of draft 12/12/12
- 1 copy draft label, date of draft 12/12/12 (highlighted)
- 1 copy CRP Certification letter
- 1 copy data matrix (confidential)
- 1 copy public data matrix
- Form 8570-34
- 1 copy data transmittal document
- 3 copies Bayer Report ID 38995
- 3 copies Bayer Report ID 38996
-

Advantage II Small Cat (11556-151)

- 1 copy proof of PRIA payment
- 1 copy Advantage II Small Cat Application for Pesticide Registration with Application Attachment
- 3 copies draft labels, date of draft 12/12/12
- 1 copy draft label, date of draft 12/12/12 (highlighted)
- 1 copy CRP Certification letter
- 1 copy data matrix (confidential)
- 1 copy public data matrix
- Form 8570-34

Advantage II Large Cat (11556-152)

- 1 copy proof of PRIA payment
- 1 copy Advantage II Large Cat Dog Application for Pesticide Registration with Application Attachment and two Appendices:
  Appendix 1 – CRP Data Review for Certification (Child Panel) – ID 38991
  Appendix 2 – CRP Data Review for Certification (Adult Panel) – ID 38992
- 3 copies draft labels, date of draft 12/12/12
- 1 copy draft label, date of draft 12/12/12 (highlighted)
- 1 copy CRP Certification letter
- 1 copy data matrix (confidential)
- 1 copy public data matrix
- Form 8570-34
- 1 copy data transmittal document
- 3 copies Bayer Report ID 38991
- 3 copies Bayer Report ID 38992

Bayer HealthCare
Animal Health

Via Federal Express

December 12, 2012

Document Processing Desk (NO REGFEE – Additional Information)
Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Bayer HealthCare LLC
Animal Health
P.O. Box 390
Shawnee Mission, KS 66201-0390

Attention: Ms. Venus Eagle (PM01)
Registration Division

Subject: Advantage II Small Cat
(EPA Reg. No. 11556-151)
Child-Resistant Packaging Certification

Dear Ms. Eagle:

I certify that the packaging (aluminum foil pouch; material# 01446067; PET/AL/PE 12/12/40) that will be used for this product meets the standard of 40 CFR 157.32.

Sincerely,

Douglas A. Spilker. Ph. D.
Manager, EPA Regulatory Affairs
Doug.Spilker@Bayer.com

ATTACHMENT FOR
APPLICATION FOR PESTICIDE REGISTRATION
December 14, 2012

Advantage II Small Cat (EPA Reg. No. 11556-151)

Purpose of Registration Action: Please find enclosed for the Agency's review and acceptance revised draft labeling, dated 12/12/12, for the subject product. The revisions to this label are only reflective of our enclosed proposal for an additional new child-resistant packaging. There have been no revisions of any efficacy claims. Please see the highlighted version of the draft label that shows the changes.

We currently have acceptable CRP packaging (designated as OPTION 1) data on file with the Agency (and the respective CRP Certification letters), but it is our desire to replace the current packaging with a different CRP packaging material (designated as OPTION 2). To do so, we also needed to revise the opening instructions. These new opening instructions were used in the enclosed Child-resistant packaging testing studies.

Packaging: Based on earlier CRP testing, the individual tubes alone did not qualify as child-resistant, and therefore were sold in child-resistant blisters. The current packaging for the products (designated as OPTION 1) has an outer cardboard carton with the tubes in a child-resistant blister. Instead of marketing the tubes in a blister pack, Bayer Animal Health would like the option (designated as OPTION 2) to market the product in a sealed "treasure chest" outer box containing a certain number (4 or 6) of single pouches (a single tube enclosed in a child-resistant pouch). The single pouches are made of aluminum foil [material# 01446067; PET/AL/PE 12/12/40] for the existing tubes.

The single-tube pouches will be packaged in one of two sizes of "treasure chest" outer boxes (4-tube pack/box dimension 108 x 34 x 120 mm or 6-tube pack/box dimension 108 x 34 168 mm). However, the component of the single pouches, the aluminum pouch (and not the tube or box), is designed to be child resistant. **Please note that there are no studies submitted for the Advantage II Small Cat (11556-151) product, since the tube size (0.4 ml) is identical to that of the Advantage II Small Dog product (11556-128); the respective studies to support this tube size are being submitted concurrently with this application with the dog submission.**

Labeling Changes: The only proposed change to the draft labeling is:

Pages 4 and 16: Addition of new opening instructions (OPTION 2) – see especially highlighted draft label.

No other substantive changes have been made to this label, except for those listed above. Therefore, as soon as the data are reviewed and found acceptable, we hope that these changes to the label can be accepted by the Agency for this product, as well as, for the revised labels of the other Advantage II cat products – Advantage II Large Cat & Advantage II Kitten - submitted concurrently with this application.

If there are any questions regarding these revisions, please contact us immediately [doug.spilker@bayer.com ; (913)-268-2751].

Pages 135-146 * Claimed confidential by submitter*

PRIA 2 – 21 Day Content Screen Review Worksheet

(EPA/OPP Use Only)

3/23/09

21 Day Screen Start Date: 12-19-2012

Experts In-Processing Signature: [signature] Date 12-26-12 Fee Paid: Yes ✓

Division management contacted on issues No_____ Yes _____ Date _____

EPA Reg. Number: 11556-151	EPA Receipt Date: 12-19-2012

	Items for Review			Yes	No	N/A*
1	**Application Form** (EPA Form 8570-1)(link to form) signed & complete including package type			X		
2	**Confidential Statement of Formula** all boxes completed, form signed, and dated (EPA Form 8570-4) (Link to form)					X
	a) All inerts (link to http://www.epa.gov/opprd001/inerts/), including fragrances, approved for the proposed uses (see Footnote A) No inerts to review	**yes**	**no**			
3	**Certification with Respect to Citation of Data** (EPA Form 8570-34) (Link to form) completed and signed (N/A if 100% repack)			X		
	Certificate and data matrix consistent			X		
	If applicant is relying on data that are compensable, is the offer to pay statement included. (see Footnote B)	**yes**	**no**			
	If applicable, is there a letter of Authorization for exclusive use only.					
4	**Formulator's Exemption Statement** (EPA Form 8570-27) (Link to form) completed and signed (N/A if source is unregistered or applicant owns the technical)					X
5	**Data Matrix** (EPA Form 8570-35) (Link to form) both internal and external copies (PR 98-5) (Link to PR 98-5) completed and signed (N/A if 100% repack)			X		
		yes	**no**			
	a) Selective Method (Fee category experts use)	X				
	b) Cite-All (Fee category experts use)					
	c) Applicant owns all data (Fee category experts use)					
6	**5 Copies of Label** (link to **http://www.epa.gov/oppfead1/labeling/lrm/**) **(Electronic labels on CD are encouraged and guidance is available)**(link to http://www.epa.gov/pesticides/regulating/registering/submissions/index.htm#labels)			X		

7	**Is the data package consistent with PR Notice 86-5** (link to PRN 86-5)			X
8	**Notice of Filing (link to http://www.epa.gov/pesticides/regulating/tolerance_petitions.htm) included with petitions (link to http://www.epa.gov/pesticides/regulating/tolerances.htm)**			X
9	**If applicable for conventional applications, reduced risk rationale (link to http://www.epa.gov/opprd001/workplan/reducedrisk.html)**			X
10	**Required Data (link to http://www.epa.gov/pesticides/regulating/data_requirements.htm) and/or data waivers. See Footnote C.**			
	a) List study (or studies) not included with application			

Comments:

- No studies submitted with submission
- No CSF submitted. —— No inerts to review.
- Amendment PASSED

LRC

MRID: NONE

* N/A – Not Applicable

Footnotes

A. During the 21 day initial content review, all CSFs will be reviewed to determine whether all inerts listed, including fragrances, are approved for the proposed uses. If an unapproved inert is identified, the applicant must either 1) resolve the inert issue by, for example, removing the inert, substituting it with an approved inert, submitting documentation that EPA approved the inert for the proposed pesticidal uses, correcting mistakes on the CSF, etc. or 2) provide the data to support OPP approval of the inert or 3) withdraw the application. Removing or substituting an inert ingredient will require a new CSF and may require submission of data. All information, forms, data and documentation resolving the inert issue must have been received by the Agency or the application withdrawn within the 21 day period, otherwise, the Agency will reject the application as described below.

To successfully complete this aspect of the 21 day initial content screen, applicants are **strongly encouraged** to verify that all inert ingredients have been approved for the application's uses **even if a product is currently registered** by consulting the inert Web

site [link to http://www.epa.gov/opprd001/inerts/lists.html] and if the inert is not approved, to **obtain the necessary inert approval prior to submitting an application to register a pesticide product containing that inert ingredient.** Some inert ingredients are no longer approved for food uses or certain types of uses. The name and/or CAS number on a CSF must match the name and CAS number on this web site. Simple typographical errors in the name or CAS number have resulted in processing delays.

If an inert is not listed on the inert ingredient web site and the applicant believes that the inert has been approved, the applicant should contact the Inert Ingredient Assessment Branch (IIAB) at inertsbranch@epa.gov and resolve the issue. Copies of the correspondence with IIAB resolving the issue should accompany the application. All new inerts except PIP inerts are reviewed by IIAB. The IIAB should also be contacted for any questions on what supporting data needs to be submitted for and the Agency's inert review process. Questions on PIP inerts should be directed to the Chief of Microbial Pesticides Branch [Link to http://www.epa.gov/oppbppd1/biopesticides/contacts_bppd.htm].

When a brand, trade, or proprietary name of an inert ingredient is listed on a CSF, additional information such as an alternate name of the inert, CAS number or other information [link to http://www.epa.gov/opprd001/inerts/tips.pdf] must also be included to enable the Agency to determine if it has been approved. Each component of an inert mixture (including a fragrance) must be identified. In some cases, the supplier of the mixture or fragrance may need to provide this information to the Agency. Prior to the Agency's receipt of an application, applicants must arrange with a proprietary mixture or fragrance supplier to provide the component information to the Agency or promptly upon EPA's request. If the inert ingredients in a proprietary blend (including fragrances) cannot or are not identified or provided within the 21-day content review period, the Agency will reject the application.

During the 21 day content review, applicants should submit information to the individual identified by the Agency when the applicant is informed of an unapproved inert.

Unapproved Inerts Identified on CSFs

All applications except conventional new products and PIPs

Once an unapproved inert is identified on a CSF, the Agency will contact the applicant with the following options:

1. Correct the application by, for instance, correcting the inert's identity or CAS number, providing documentation that the inert has been approved, or removing the unapproved inert from the CSF or replacing it with one that is approved for the application's uses; or

2. Submit the information and data needed for the Agency to approve the unapproved inert. If this option is selected and implemented, the Agency may request an extension in the PRIA decision review timeframe to accommodate the inert review/approval process;

3. Withdraw the application (the Agency retains 25% of the full fee for the fee category estimated); or

If none of these options is selected and implemented by the applicant within the 21 day content review period, the Agency will reject the application and retain 25% of the full fee of the category identified.

Conventional New Product Applications

When the Registration Division identifies an unapproved inert on a CSF with an application for a new product that the applicant has not identified as requiring an inert approval (R311, R312 or R313), it will contact the applicant with the following options:

1. Correct the application by, for instance, correcting the inert's identity or CAS number, providing documentation that the inert has been approved, or removing the unapproved inert from the CSF or replacing it with one that is approved for the application's uses; or

2. Submit the information and data needed for the Agency to approve the unapproved inert, including any required petition to establish or amend a tolerance or exemption from a tolerance. (This option may change the PRIA category for the application, which could require a longer decision review time and a larger fee. If additional fees are due, they must be received by the Agency within the 21 day content review period.)

3. Withdraw the application (the Agency retains 25% of the full fee for the fee category estimated); or

If none of the above options is selected and implemented during the 21-day content-review period, the Agency will reject the application and retain 25% of the appropriate fee for the new product-inert approval category.

PIP Applications

When the Biopesticide and Pollution Prevention Division identifies an unapproved inert on a PIP CSF and a request to approve the inert does not accompany the application, it will contact the applicant with the following options:

1. Correct the application by, for instance, correcting the spelling or name of the inert to that in 40 CFR 174, or providing documentation that the inert has been approved; or

2. Submit the information and data needed for the Agency to approve the unapproved inert. If an inert ingredient tolerance exemption petition is required, the petition must be received by the Agency and the B903 fee paid within the 21 day period. If this option is selected and implemented, the Agency will discuss harmonizing the timeframe for both actions.

3. Withdraw the application (the Agency retains 25% of the full fee for the fee category estimated); or

If none of the above options is selected and implemented during the 21 day content review period, the Agency will reject the application and retain 25% of the fee.

B. A policy on documentation of offers to pay is still being developed, however, for a me-too or fast track (similar/identical) new product, R300 or A530, an application without the necessary authorizations of offers to pay will be placed into either R301 or A531. The Agency recommends that authorizations of offers to pay be submitted with other PRIA applications to avoid delays in the Agency's decision.

C. Biopesticide applicants are advised to contact the Agency and discuss study waivers prior to submitting their application to the Agency. Documentation of such discussions should be submitted with the study waiver.

Script for Rejection Phone calls

Contact Name: Douglas A. Spilker
Phone #: (913) 208-2751
Email: Doug.Spilker@Bayer.com

First Call/Initials: LC	**Second Call/Initials:**
Date: 12/27/12	**Date:**
Time: 2:45pm	**Time:**

This is Leah M. Correa **, EPA contractor.**

I'm calling regarding your submission in support of
Advantage II Small Cat (EPA REG#: 11550-151)

We have found the following deficiencies regarding:
PR Notice 2011-3: Yes or No
Volume/Study Title:

Volume/Study Title:

Volume/Study Title:

Additional volumes continued on back of page: Yes or No

Application Package: Yes or No
- The internal and external copy of the data matrix needs to be signed on each page

These deficiencies have been approved by EPA.
The corrections can be faxed to 703-305-5060/Attn: Leah M. Correa .

Second Call/Email:
If we do not receive the corrections by 1/2/13 **, we will process your submission, accordingly. Please direct all future calls and correspondence to the appropriate EPA Risk Manager.**

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

December 21, 2012

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

OPP Decision Number: D-473349
EPA File Symbol or Registration Number: 11556-151
Product Name: ADVANTAGE II SMALL CAT
EPA Receipt Date: 19-Dec-2012
EPA Company Number: 11556
Company Name: BAYER HEALTHCARE LLC

DOUGLAS A. SPILKER
BAYER HEALTHCARE LLC
ANIMAL HEALTH DIVISION
PO Box 390
SHAWNEE MISSION, KS 66201-0390

SUBJECT: Receipt of Registration Amendment Subject to Registration Service Fee

Dear Registrant:

The Office of Pesticide Programs has received your amendment and certification of payment. If you submitted data with this application, the results of the PRN-2011-3 screen will be communicated separately. During the administrative screen, the Office of Pesticide Programs has determined that this Action is subject to a Pesticide Registration Service Fee as defined in the Pesticide Registration Improvement Act.

The Action has been identified as Action Code: R340

AMENDMENT;NON-FAST TRACK;REVIEW WITHIN RD, E.G. PRECAUTIONARY LABELING;

No additional payment is due at this time.

If you have any questions, please contact the Pesticide Registration Service Fee Ombudsman at (703) 308-9362.

Sincerely,

Front End Processing Staff
Information Technology & Resources Management Division

Fee for Service

{928410u~

This package includes the following

- ○ New Registration
- ◉ Amendment

☐ Studies? ☐ Fee Waiver?

☐ volpay % Reduction: ___

for Division

- ○ AD
- ○ BPPD
- ◉ RD

Risk Mgr. 1

Receipt No. S- 928410

EPA File Symbol/Reg. No. 11556-151

Pin-Punch Date: 12/20/2012

☐ This item is NOT subject to FFS action.

Action Code:

Requested: R340

Granted: R340

Amount Due: $ 3617

Parent/Child Decisions:

☐ Inert Cleared for Intended Use ☐ Uncleared Inert in Product

Reviewer: E. Fertich Date: 12/21/12

Remarks:

Doug Spilker

From: paygovadmin@mail.doc.twai.gov
Sent: Thursday, December 13, 2012 8:05 AM
To: Doug Spilker
Subject: Pay.gov Payment Confirmation: PRIA Service Fees

Your payment has been submitted to Pay.gov and the details are below. If you have any questions regarding this payment, please contact Pay.gov Customer Service by phone at (800) 624-1373 or by email at pay.gov.clev@clev.frb.org.

Application Name: PRIA Service Fees
Pay.gov Tracking ID: 258TINNN
Agency Tracking ID: 74387644153
Transaction Type: Sale
Transaction Date: Dec 13, 2012 9:05:12 AM

Account Holder Name: Douglas A. Spilker
Transaction Amount: $3,617.00
Billing Address: 12707 Shawnee Mission Parkway
City: Shawnee
State/Province: KS
Zip/Postal Code: 66216
Country: USA
Card Type: MasterCard
Card Number: **********0576

Decision Number:
Registration Number: 11556-151
Company Name: Bayer HealthCare, LLC-AH
Company Number: 11556
Action Code: R340

THIS IS AN AUTOMATED MESSAGE. PLEASE DO NOT REPLY.

21-Day Screen of Amendment
(Completed by Contractor)

21-day Expires on 1/9/13

Document Part Of: 11556-151
MRID, If Any: _____

Content Screen: Recommended to Pass/Fail

11-3 Review: Passed/Failed/NA

Overall Status: Pass/Fail

Document returned to:

Steve Schaible

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

JAN 10 2013

Dr. Douglas A. Spilker
Bayer Healthcare LLC
Animal Health Division
P.O. Box 390
Shawnee Mission, KS 66201-0390

Subject: Notice of Extension of Conditional Registrations until January 17, 2015

Dear Dr. Spilker:

This letter is in reference to your applications dated November 28, 2012, in which you request to extend the following, conditional registrations:

Advantage II Medium Dog	EPA Reg. No. 11556-125
Advantage II Large Dog	EPA Reg. No. 11556-127
Advantage II Small Dog	EPA Reg. No. 11556-128
Advantage II Extra Large Dog	EPA Reg. No. 11556-130
Advantage II Kitten	EPA Reg. No. 11556-150
Advantage II Small Cat	EPA Reg. No. 11556-151
Advantage II Large Cat	EPA Reg. No. 11556-152

The above-referenced registrations contain conditions calling for the registrations to expire two years from the date the products are first released for shipment (i.e., January 17, 2013). Additionally, Bayer is required to adhere to the spot on label mitigation, and to submit quarterly enhanced incident reports and quarterly sales information for each of the above registrations.

The Agency has found Bayer to be in compliance with the terms and conditions for the subject products, and is therefore is granting the request to extend the 2-year time-limited registration restrictions. As such, the following changes are being made to the terms and conditions for the products listed above:

- **The 2-year time-limited registration restrictions have been extended for an additional 2 years. The new expiration dates for the registrations listed above are January 17, 2015.**

Please note that these products are still subject to all other previously required conditions of registration. If Bayer wishes to remove the time limitations altogether, please submit to the Product Manager an amendment application for each product to change the terms and conditions of the registration. Please include with your submission a written rationale for the removal of the time limitation. As you remember, the Agency included this time limitation as a condition of registration for your products to allow for the post-market surveillance[1] of these products. Therefore, we recommend that you include in your rationale the following information, along with any additional information or analyses you think would be helpful to the agency (e.g., tables, charts, information on stewardship activities, etc...):

- A summary and analysis of the incidents received associated with these products, including information on the following:
  - A comprehensive analysis of incident rates per doses distributed;
  - An analysis of historical incident trends since the products' release into the marketplace;
  - An analysis of historical incident trends by weight range of animal, breed, weight range of product, etc...
- If these products are also registered in the European Union or Canada, information on incident rates per doses distributed and trends in those countries.

Please also note that requests to remove the expiration date condition are not subject to PRIA fees and do not have to be submitted under PRIA. However, these would also not be considered 90-day, fast-track submissions in order to allow the EPA enough time to fully evaluate the information provided. After receiving these submissions, the EPA will consider the incidents received since the initial registration; review the information and rationale provided; and make a decision on the request.

If you have any questions, please contact the product manager, Venus Eagle, at eagle.venus@epa.gov or (703) 308-8045.

Regards,

Venus Eagle for

Meredith Laws, Chief
Insecticide-Rodenticide Branch
Registration Division (7505P)

[1] http://www.epa.gov/pesticides/health/spot-on-meetings.html

FAST-TRACK AMENDMENTS – Completeness Screening Checklist

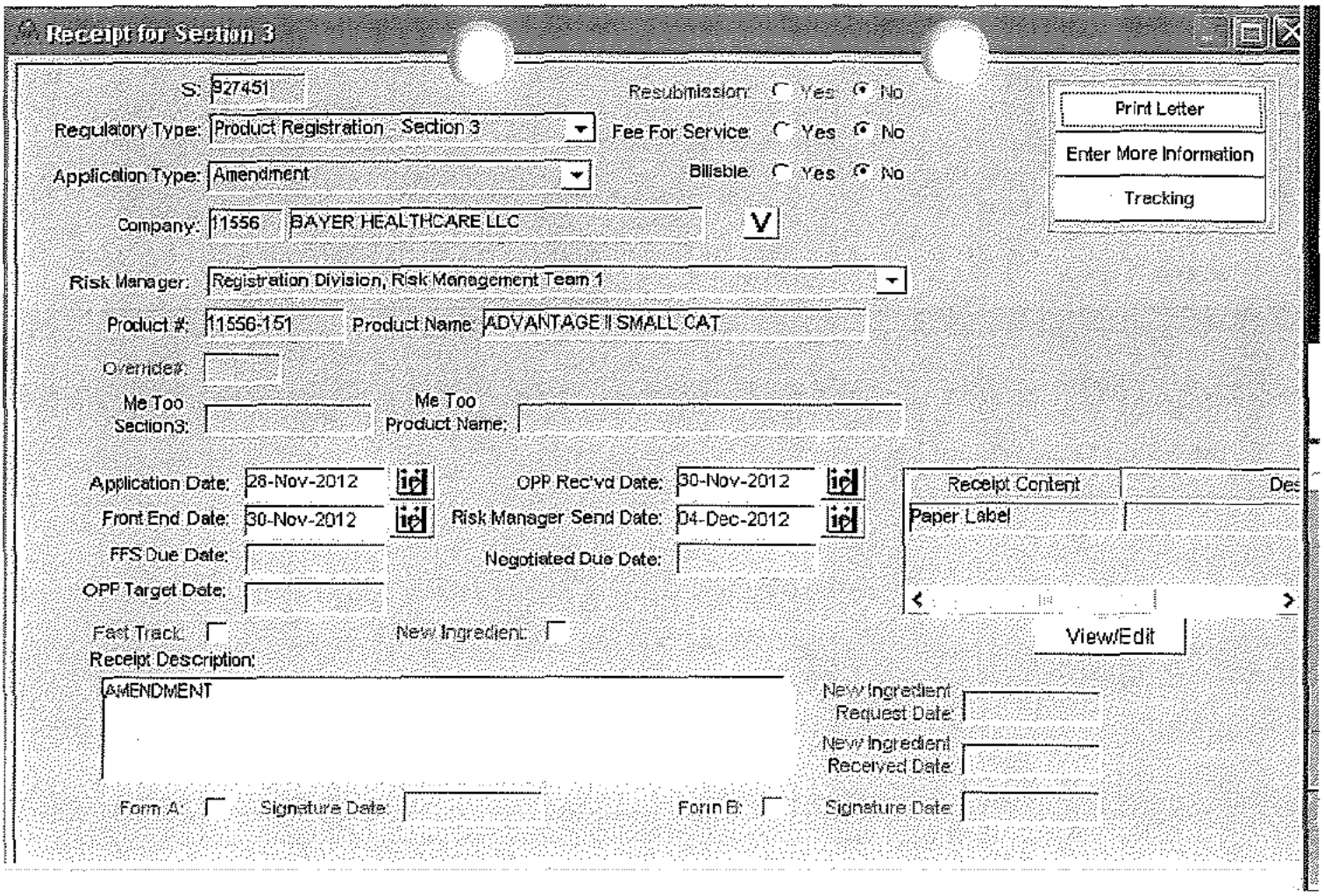
Expert's In-Processing Signature: KV Date: 12-6-12 PM #: 1

EPA Reg. Number: 11556 -150 -151 -152	EPA Receipt Date: 11-30-12

	Checklist Item	Yes	No	N/A
1	**Application Form** (EPA Form 8570-1) - signed?	✓		
2	**Confidential Statement of Formula** (EPA Form 8570-29) - signed?			
3	**Certification with Respect to Citation of Data** (EPA Form 8570-34) - signed?			
4	**Formulator's Exemption Statement** (EPA Form 8570-27) - signed?			
5	**Data Matrix** (EPA Form 8570-35) [Applicable for adding me-too uses] - signed?			
	a) Selective Method?			
	b) Cite-All Method?			
	c) Public copy of Matrix provided? See PR Notice 98-5			
6	**Is Label included?** (5 copies)	✓		
	a) Electronic Label submitted?		✓	

Comments:

Set of 3


Receipt for Section 3
S: 927451
Resubmission: Yes No
Regulatory Type: Product Registration Section 3
Fee For Service: Yes No
Application Type: Amendment
Billable: Yes No
Company: 11556 BAYER HEALTHCARE LLC
Print Letter
Enter More Information
Tracking
Risk Manager: Registration Division, Risk Management Team 1
Product #: 11556-151
Product Name: ADVANTAGE II SMALL CAT
Override#:
Me Too Section3:
Me Too Product Name:
Application Date: 28-Nov-2012
OPP Rec'vd Date: 30-Nov-2012
Front End Date: 30-Nov-2012
Risk Manager Send Date: 04-Dec-2012
FFS Due Date:
Negotiated Due Date:
OPP Target Date:
Receipt Content
Paper Label
Fast Track:
New Ingredient:
View/Edit
Receipt Description:
AMENDMENT
New Ingredient Request Date:
New Ingredient Received Date:
Form A:
Signature Date:
Form B:
Signature Date:

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

December 4, 2012

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DR. BRUCE MARTIN
BAYER HEALTHCARE LLC
ANIMAL HEALTH DIVISION
PO Box 390
SHAWNEE MISSION, KS 66201-0390

PRODUCT NAME: ADVANTAGE II SMALL CAT
COMPANY NAME: BAYER HEALTHCARE LLC
OPP IDENTIFICATION NUMBER:
EPA FILE SYMBOL: 11556-151
EPA RECEIPT DATE: 11/30/12

SUBJECT: RECEIPT OF AMENDMENT

DEAR REGISTRANT:

The Office of Pesticide Programs has received your application for an amendment and it has passed an administrative screen for completeness.

During the initial screen we determined that the application appears to qualify for fast track review. The package will now be forwarded to the Product Manager for review to determine its acceptability for fast track status.

If you have any questions, please contact Registration Division, Risk Management Team 1, at (703) 308-8045.

Sincerely,

Front End Processing Staff
Information Services Branch
Information Technology & Resources Management Division

Fee for Service {927451%~

This package includes the following

- ○ New Registration
- ◉ Amendment

☐ Studies? ☐ Fee Waiver?

☐ volpay % Reduction: ___

for Division

- ○ AD
- ○ BPPD
- ◉ RD

Risk Mgr. 1

Receipt No. S- 927451

EPA File Symbol/Reg. No. 11566-151

Pin-Punch Date: 11/30/2012

☑ This item is NOT subject to FFS action.

Action Code:

Requested:

Granted:

Amount Due: $ _____

Parent/Child Decisions:

☐ Inert Cleared for Intended Use ☐ Uncleared Inert in Product

Reviewer: _____ Date: 12-4-12

Remarks:

Bayer HealthCare
Animal Health

Via Federal Express

November 28, 2012

Document Processing Desk (Non-PRIA Action)
Office of Pesticide Programs (7505P)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Attention: Ms. Venus Eagle/PM 01

Bayer HealthCare LLC
Animal Health
P.O. Box 390
Shawnee Mission, KS 66201-0390

Subject: ***Request for Extension of Time-limited Registrations for the following products:***
Advantage II Kitten (EPA Reg. No. 11556-150)
Advantage II Small Cat (EPA Reg. No. 11556-151)
Advantage II Large Cat (EPA Reg. No. 11556-152)

Dear Ms. Eagle:

Reference is made to the current registrations of the subject products, and the Agency's letter to us, dated September 20, 2011 (received October 11, 2011), regarding "Implementation of Label Changes to Pet Spot-on Products." In that letter, certain actions were required by us, the registrant, to maintain these registrations. These registrations were designated as "Time-limited" with **an expiration date of January 17, 2013.** Since we have complied with the conditions of the aforementioned Agency letter, we request an extension of these registrations, until such time as to allow us to pursue the complete removal of the time limitations.

The Agency has now accepted draft labeling for Advantage II Kitten (dated 09/25/2012), for Advantage II Large Cat (dated 9/25/12) and Advantage II Small Cat (dated 11/07/12) with the appropriate revisions outlined in the aforementioned EPA "Implementation" letter, and subsequent requests of the Agency. Also as required, we submitted the respective printer's proofs of each of the elements of the Final Printed Labeling (packaging) for these products.

Furthermore, we have submitted the required quarterly enhanced incident reports for these products beginning with the products' initial releases for shipment (6 quarters). Adverse incident reports have been and continue to be monitored in accordance to the stipulations of the conditional registration. Analysis of the accumulated incident reporting for the initial eighteen (18) months of commercial distribution of the Advantage II Cat registrations indicate occurrence rates to range from rare to very rare. Actual rates (expressed as the ratio incident : doses sold) were 1:7,249, 1:10,924 and 1:8,440 for the Kitten, Small Cat and Large Cat respectively.

Since we have complied with the conditions of the aforementioned Agency's letter to us, dated September 20, 2011, we request an extension of these registrations as soon as possible, since these registrations have an **expiration date of January 17, 2013.** Enclosed are additional draft copies of the EPA stamped-accepted labels for these products (only the internal version code and date of draft has changed) for your use in processing this request.

In a separate submission, we will be provide an analysis of the submitted enhanced incident reports of these products showing that there is no longer a need for these products to have time-limited registrations based on the safe use history of these products on the respective companion animals.

If you have any questions, please do not hesitate to call (913-268-2751).

Sincerely,

Douglas A. Spilker. Ph. D.
Manager, EPA Regulatory Affairs
Doug.Spilker@Bayer.com

Enclosures:

1) Advantage II Kitten - Application
2) Advantage II Kitten - Draft label, dated 11/28/12 (1 copy)
3) Advantage II Small Cat - Application
4) Advantage II Small Cat - Draft label, dated 11/28/12 (1 copy)
5) Advantage II Large Cat - Application
6) Advantage II Large Cat - Draft label, dated 11/28/12 (1 copy)

Please read instructions on reverse before completing form.

Form Approved. OMB No. 2070-0060

United States
Environmental Protection Agency
Washington, DC 20460

[ ] Registration
[X] Amendment
[ ] Other

OPP Identifier Number

Application for Pesticide - Section I

1. Company/Product Number	2. EPA Product Manager	3. Proposed Classification
11556-151	Venus Eagle	[X] None [ ] Restricted
4. Company/Product (Name)	**PM#**	
Advantage II Small Cat	01	

5. Name and Address of Applicant *(Include ZIP Code)*

Bayer Healthcare LLC, Animal Health Division
P.O. Box 390
Shawnee Mission, KS 66201-0390

[ ] *Check if this is a new address*

6. Expedited Reveiw. In accordance with FIFRA Section 3(c)(3)(b)(i), my product is similar or identical in compositian and labeling to:

EPA Reg. No. _____

Product Name _____

Section - II

[X] Amendment - Explain below.
[ ] Resubmission in response to Agency letter dated _____
[ ] Notification - Explain below.
[ ] Final printed labels in repsonse to Agency letter dated _____
[ ] "Me Too" Application.
[ ] Other - Explain below.

Explanation: Use additional page(s) if necessary. (For section I and Section II.)

Non-PRIA Action: Bayer has complied with the conditions of the Agency's letter, dated September 20, 2011, and therefore requests a time extension of this registration as soon as possible, since it has an expiration date of January 17, 2013. Enclosed is a draft copy of the EPA stamped-accepted label for this product (only the internal version code and date of draft has changed) for your use in processing this request. Please see cover letter of 11/28/12 for more details. Email Contact: doug.spilker@bayer.com

Section - III

1. Material This Product Will Be Packaged In:

Child-Resistant Packaging	Unit Packaging	Water Soluble Packaging	2. Type of Container
[ ] Yes [ ] No	[ ] Yes [ ] No	[ ] Yes [ ] No	[ ] Metal [ ] Plastic [ ] Glass [ ] Paper [ ] Other (Specify)
* ***Certification must be submitted***	If "Yes" Unit Packaging wgt. / No. per container	If "Yes" Package wgt / No. per container	

3. Location of Net Contents Information	4. Size(s) Retail Container	5. Location of Label Directions
[ ] Label [ ] Container		

6. Manner in Which Label is Affixed to Product: [ ] Lithograph [ ] Paper glued [ ] Stenciled [ ] Other _____

Section - IV

1. Contact Point *(Complete items directly below for identification of individual to be contacted, if necessary, to process this application.)*

Name	Title	Telephone No. (Include Area Code)
Douglas A. Spilker, Ph.D.	Manager, EPA Reg. Affairs	913-268-2751

Certification

I certify that the statements I have made on this form and all attachments thereto are true, accurate and complete. I acknowledge that any knowlingly false or misleading statement may be punishable by fine or imprisonment or both under applicable law.

6. Date Application Received (Stamped)

2. Signature	3. Title
[signature]	Manager, EPA Reg. Affairs
4. Typed Name	**5. Date**
Douglas A. Spilker, Ph.D.	28 Nov. 2012

EPA Form 8570-1 (Rev. 3-94) Previous editions are obsolete. White - EPA File Copy (original) Yellow - Applicant Copy

Material Sent for Data Extraction

Reg. # 11556-151

Description: _____

☐ Material(s) Sent to Data Extraction Contractors:

- ☑ New Stamped Label Dated 10/25/12
- ☐ Notification Dated _____
- ☐ New CSF(s) Dated _____
- ☐ Other: _____

☐ Decision #: _____

☐ Other Action/Comments: _____

_____

File this coversheet and attached materials in the jacket. It must be well organized and clipped together, NOT STAPLED. Then give the jacket with the coversheet and materials to staff in the Information Services Center (ISC) (Room S-4900). If a jacket is full or only available as an image, please file materials in a new jacket and bring it down to the (ISC). For further information please call 703-605-0716.

Reviewer: Autumn Metzger

Phone: 305-5314 Division: RD - IRB

Date: 12/27/12

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OCT 25 2012

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

Douglas Spilker, Ph.D
Bayer HealthCare LLC, Animal Health Division
P.O. Box 390
Shawnee Mission, KS 66201-0390

Dear Dr. Spilker:

Subject: Amendment to update labels per spot on mitigation letter sent by the Agency dated September 30, 2011
EPA Registration Nos./Product name:
11556-150, Advantage II Kitten
11556-151, Advantage II Small Cat
11556-152, Advantage II Large Cat

The labeling referred to above submitted in connection with the Federal Insecticide, Fungicide and Rodenticide, as amended are acceptable.

As a reminder, **this registration** is **time-limited** and **expires January 17, 2013**. You must apply to extend the expiration and/or to change the terms of this registration.

Per the implementation of label changes for pet spot on products, the Agency has reviewed a copy of the print ready label

A stamped copy of the labeling is enclosed for your records. If you have any questions regarding this label, please contact Autumn Metzger at (703) 305-5314.

Sincerely,

Venus Eagle

Venus Eagle
Product Manager 01
Insecticide-Rodenticide Branch
Registration Division (7505P)

Reason To Issue:	Revise according to EPA "Implementation of Label Changes to Pet Spot-On Products" document	Date: 09/25/12 Supersedes: 03/26/12 and 09/15/10

NOTE TO REVIEWER: [(Brackets and parentheses indicate alternate language)]

[Front Panel]

Advantage® II Small Cat

Once-A-Month Topical Flea Prevention and Treatment for Cats
For Use ONLY on Cats 8 Weeks and Older and Weighing 5 - 9 lbs.

[Selected optional claims bulleted here from page 10 and/or 11]

-
-
-
-

Active Ingredients	% By Weight
Imidacloprid	9.10%
Pyriproxyfen	0.46%
Other Ingredients	90.44%
Total	100.00%

EPA Est. No. 11556-XXX-X EPA Reg No. 11556-151

KEEP OUT OF REACH OF CHILDREN

CAUTION

See back panel for Precautionary Statements.
For Directions for Use, Storage and Disposal, and First Aid see package insert inside.

ACCEPTED
OCT 25 2012
Under the Federal Insecticide, Fungicide, and Rodenticide Act, as amended, for the pesticide registered under:

EPA. Reg. No: 11556-151

Reason To Issue:	Revise according to EPA "Implementation of Label Changes to Pet Spot-On Products" document	Date: Supersedes:	09/25/12 03/26/12 and 09/15/10

[Back Panel]

Advantage® II Small Cat

Once-A-Month Topical Flea Prevention and Treatment for Cats
For Use ONLY on Cats 8 Weeks and Older and Weighing 5 - 9 lbs.

READ THE ENTIRE LABEL BEFORE EACH USE
For the Prevention and Treatment of Flea Infestations

PRECAUTIONARY STATEMENTS

HAZARDS TO HUMANS

CAUTION: Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling. Keep out of reach of children. Do not contaminate feed or food.

HAZARDS TO DOMESTIC ANIMALS

For external use only. Do not apply to cats or kittens under 8 weeks of age or weighing less than 5 lbs. As with any product, consult your veterinarian before using this product on debilitated, aged, pregnant or nursing cats. Individual sensitivities, while rare, may occur after using ANY pesticide product for cats. If signs persist, or become more severe, consult a veterinarian immediately. If your cat is on medication, consult your veterinarian before using this or any other product.

Side Effects: Monitor your cat after application. Side effects, although very rare, may include signs of skin irritation such as redness, scratching, or other signs of discomfort. Gastrointestinal signs such as hypersalivation, vomiting or diarrhea have also been reported. If these or other side effects (such as lethargy) occur, consult your veterinarian or call 1-800-422-9874.

For consumer questions call 1-800-255-6826.
For medical emergencies call 1-800-422-9874.

RESTRICTIONS:

- Use only on cats or kittens 8 weeks and older and weighing 5 – 9 lbs. Do not use on other animals.
- Do not apply more than one (1) tube per treatment.
- Do not have contact or allow children to have contact with treated area until completely dry.

Reason To Issue:	Revise according to EPA "Implementation of Label Changes to Pet Spot-On Products" document	Date: Supersedes:	09/25/12 03/26/12 and 09/15/10

Net Contents: [X] Tube(s), each 0.014 fl. oz. (0.4 mL)

[Sample - Not for (Re)Sale]

Manufactured For

Bayer HealthCare LLC
Animal Health Division
P.O. BOX 390
Shawnee Mission, Kansas 66201 USA

Made in Germany

Reason To Issue:	Revise according to EPA "Implementation of Label Changes to Pet Spot-On Products" document	Date: 09/25/12 Supersedes: 03/26/12 and 09/15/10

[Back Panel and/or Insert]

Advantage® II Small Cat

Once-A-Month Topical Flea Prevention and Treatment for Cats
For Use ONLY on Cats 8 Weeks and Older and Weighing 5 - 9 lbs.

READ THE ENTIRE LABEL BEFORE EACH USE
For the Prevention and Treatment of Flea Infestations

DIRECTIONS FOR USE

It is a violation of Federal Law to use this product in a manner inconsistent with its labeling.

HOW TO OPEN

1. Being careful not to cut close to the blister cavities, take scissors and cut off one section of the card containing a single tube.
2. Take the separated section, and cut into the blister cavity across the small side, close to the cap of the tube.
3. Peel off the foil, and take out the tube.
4. Repeat steps 1 to 3 for each tube.

HOW TO APPLY

1. Remove one applicator tube from the package. See "HOW TO OPEN" section.

2. Hold applicator tube in an upright position facing away from you and your pet's face and eyes. Pull cap off tube.

[Visuals Depicting How to Open Applicator Tube]

3. Turn the cap around and place other end of cap back on tube.

4. Twist cap to break seal, then remove cap from tube.

5. Part the hair on the neck at the base of the skull until the skin is visible. Place the tip of the tube on the skin and squeeze the tube to expel the entire contents directly on the skin. *Do not get this product in your cat's eyes, or allow your cat to ingest this*

product. The product is bitter tasting and salivation may occur for a short time if the cat licks the product immediately after treatment. Treatment at the base of the skull will minimize the opportunity for the cat to lick the product. Do not allow the product to run off.

[Visuals Depicting Application to Animal]

6. Discard empty tube as described in Storage and Disposal.

7. Under normal conditions this product is effective for a month. However, in case of severe flea infestation, retreatment may be necessary earlier than four (4) weeks. Do not retreat more often than once every seven (7) days. After flea control is attained, return to a monthly retreatment schedule.

PRODUCT INFORMATION

The successive feeding activity of fleas on cats frequently elicits a hypersensitivity skin disorder known as flea allergy dermatitis (FAD) or flea bite hypersensitivity. Treatment of cats with Advantage® II Small Cat kills fleas and may reduce the incidence of this condition.

Advantage® II Small Cat kills the existing fleas on cats within 12 hours. Reinfesting fleas are killed within 2 hours with protection against further flea infestation lasting for up to four (4) weeks. Pre-existing pupae in the environment may continue to emerge for six (6) weeks or longer depending upon the climatic conditions.

Fleas, eggs and larvae in the cat's surroundings are killed following contact with an Advantage® II Small Cat treated cat. Advantage® II Small Cat provides multi-stage flea control effectively breaking all flea life-cycle stages for lasting control of flea populations.

Advantage® II Small Cat kills adult fleas quickly, within 12 hours, inhibits the development of immature flea life stages and prevents them from reaching the biting adult stage.

Advantage® II Small Cat is waterproof and remains effective following a shampoo treatment or after exposure to rain or sunlight.

Apply monthly treatments for optimal control and prevention of fleas.

KEEP OUT OF REACH OF CHILDREN

CAUTION

PRECAUTIONARY STATEMENTS
HAZARDS TO HUMANS

CAUTION: Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling. Keep out of reach of children. Do not contaminate feed or food.

FIRST AID	
If Swallowed:	• Call a poison control center or doctor immediately for treatment advice. • Have person sip a glass of water if able to swallow. • Do not induce vomiting unless told to do so by the poison control center or doctor. • Do not give anything to an unconscious person.
If In Eyes:	• Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. • Call a poison control center or doctor for treatment advice.
If On Skin	• Wash with plenty of soap and water.
HOT LINE NUMBER	
Have the product container or label with you when calling a poison control center or doctor, or going for treatment. For medical emergencies call 1-800-422-9874. For customer questions call 1-800-255-6826.	
NOTE TO PHYSICIAN	
Treat the patient symptomatically.	

HAZARDS TO DOMESTIC ANIMALS

For external use only. Do not apply to cats or kittens under 8 weeks of age or weighing less than 5 lbs. As with any product, consult your veterinarian before using this product on debilitated, aged, pregnant or nursing cats. Individual sensitivities, while rare, may occur after using ANY pesticide product for cats. If signs persist, or become more severe, consult a veterinarian immediately. If your cat is on medication, consult your veterinarian before using this or any other product.

Side Effects: Monitor your cat after application. Side effects, although very rare, may include signs of skin irritation such as redness, scratching, or other signs of discomfort. Gastrointestinal signs such as hypersalivation, vomiting or diarrhea have also been reported. If these or other side effects (such as lethargy) occur, consult your veterinarian or call 1-800-422-9874.

For consumer questions call 1-800-255-6826.
For medical emergencies call 1-800-422-9874.

RESTRICTIONS:

- Use only on cats or kittens 8 weeks and older and weighing 5 – 9 lbs. Do not use on other animals.
- Do not apply more than one (1) tube per treatment.
- Do not have contact or allow children to have contact with treated area until completely dry.

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal.

Pesticide Storage: Store in a cool, dry place inaccessible to children and pets. **Pesticide Disposal and Container Handling:** Nonrefillable container. **If empty**: Do not reuse or refill this container. Place in trash or offer for recycling if available. **If partly filled**: Call your local solid waste agency or 1-800-422-9874 for disposal instructions. Never place unused product down any indoor or outdoor drain.

LIMITED WARRANTY AND LIMITATION OF DAMAGES

Bayer HealthCare LLC, Animal Health Division warrants that this material conforms to the chemical description on the label. TO THE EXTENT CONSISTENT WITH APPLICABLE LAW, BAYER MAKES NO OTHER EXPRESS OR IMPLIED WARRANTY, INCLUDING ANY OTHER EXPRESS OR IMPLIED WARRANTY OF FITNESS OR MERCHANTABILITY, and no agent of Bayer is authorized to do so except in writing with a specific reference to this warranty. Any damages arising from a breach of this warranty shall be limited to direct damages and shall not include consequential commercial damages such as loss of profits or values, etc.

Reason To Issue:	Revise according to EPA "Implementation of Label Changes to Pet Spot-On Products" document	Date: Supersedes:	09/25/12 03/26/12 and 09/15/10

[Label on Individual Tube]

Advantage® II Small Cat

9.10% Imidacloprid

0.46% Pyriproxyfen

0.014 fl. oz. (0.4 mL)

EPA Reg. No. 11556-151

Keep Out of Reach of Children

CAUTION

Read The Entire Label Before Use

BAYER

Lot No. 0000000

Reason To Issue:	Revise according to EPA "Implementation of Label Changes to Pet Spot-On Products" document	Date: Supersedes:	09/25/12 03/26/12 and 09/15/10

[Label on blister card; one card containing 1, 2, 3, 4, 5, or 6 tubes]

Advantage® II Small Cat

For external use only on cats and kittens 8 weeks and older and weighing 5 - 9 lbs.

9.10% Imidacloprid

0.46% Pyriproxyfen

[X] - 0.014 fl. oz. (0.4 mL)

EPA Reg. No. 11556-151

BAYER

Reason To Issue:	Revise according to EPA "Implementation of Label Changes to Pet Spot-On Products" document	Date: 09/25/12 Supersedes: 03/26/12 and 09/15/10

NOTE TO REVIEWER: [(Brackets and parentheses indicate alternate language)]

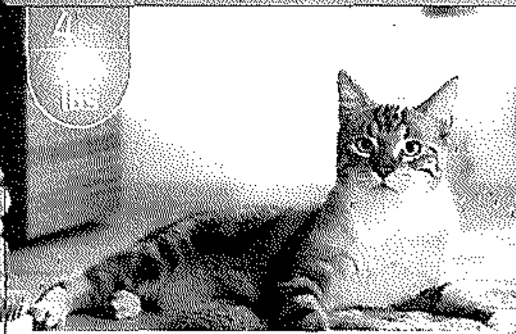
OPTIONAL MARKETING CLAIMS [Appearing on any panel[

- For use on cats and kittens 8 weeks of age and older
- Advantage II contains [imidacloprid], [and an/the] [insect growth regulator] [IGR] [pyriproxyfen]
- A single topical application remains effective for up to [4 weeks] [a month]
- Convenient, easy-to-apply topical solution
- Convenient, easy-to-apply and fragrance free [monthly] [topical solution]
- Once a month topical flea prevention and treatment for cats 8 weeks of age or older
- Advantage II is indicated for the prevention and treatment of fleas on cats 8 weeks of age and older
- For the prevention and treatment of flea infestations
- One treatment prevents further flea infestations for up to [4 weeks] [a month]
- Kills fleas on cats within [12] hours and continues to prevent infestations for up to [four weeks] [a month]
- Kills fleas before they lay eggs
- Larval flea stages in the cat's environment are killed following contact with an Advantage II treated cat
- Kills larval stages of fleas following contact with an Advantage II treated cat
- Kills fleas within [12] hours of application
- Stops existing flea infestations by killing adult fleas
- Prevents reinfestations by killing adult fleas before they lay eggs
- Reinfesting fleas are killed within 2 hours with protection against further flea infestation
- [Prevents] [Stops] flea eggs from hatching [into biting adults]
- Effectively breaks the flea life cycle
- [Kills] [Controls] all flea life stages
- Comprehensive flea prevention and treatment
- 3-way flea protection ([kills] [controls]) adults, larvae, and eggs
- [Prevents] [Stops] flea eggs from developing into [(biting) (adult)] fleas
- Treatment with Advantage II kills fleas and may reduce the incidence of flea allergic dermatitis [FAD] or flea bite hypersensitivity
- Flea adulticide, larvicide, and ovicide
- Kills flea eggs
- Controls flea problems
- Provides flea protection
- Controls existing fleas and flea eggs plus [and] [prevents] future flea infestations
- Advantage II may be used year-round for flea [prevention][protection]

- Contains an insect growth regulator (IGR) to kill flea eggs and prevent re-infestation
- Monthly use of Advantage II kills fleas and may prevent ([flea allergy dermatitis][flea bite hypersensitivity])
- Controls existing flea infestations on your cat and prevents further infestations
- Prevents fleas on treated cats from infesting (reinfesting)
- Remains effective after bathing
- Remains effective following shampooing
- Waterproof
- Remains effective after exposure to rain or sunlight
- Fragrance-free
- In child-resistant packaging
- Starts working through contact

advantage® II

small cat



Once-A-Month Topical Flea Prevention and Treatment for Cats

For Use ONLY on Cats 8 Weeks and Older and Weighing 5 – 9 lbs.

- Kills all flea life stages
- Controls existing flea infestations on your cat and prevents further infestations
- Kills fleas within 12 hours of application

Active Ingredients	% By Weight
Imidacloprid	9.10%
Pyriproxyfen	0.46%
Other Ingredients	90.44%
Total	100.00%

Net Contents: 4 Tubes, each 0.014 fl. oz. (0.4 ml)

KEEP OUT OF REACH OF CHILDREN

CAUTION

See back panel for Precautionary Statements. For Directions for Use, Storage and Disposal, and First Aid, see package insert inside.

4

Fleas | Flea Eggs | Flea Larvae | Waterproof

Bayer

advantage II small cat

recycled paper 90%

2 24089-61669 2

105x25x165

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advantage II

small cat

Once-A-Month Topical Flea Prevention and Treatment for Cats

For Use ONLY on Cats 8 Weeks and Older and Weighing 5–9 lbs.

READ THE ENTIRE LABEL BEFORE EACH USE

For the Prevention and Treatment of Flea Infestations:
- Kills flea adults, larvae and eggs
- Controls existing flea infestations on your cat and prevents further infestations
- Kills fleas within 12 hours of application

PRECAUTIONARY STATEMENTS

HAZARDS TO HUMANS

CAUTION: Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling. Keep out of reach of children. Do not contaminate feed or food.

HAZARDS TO DOMESTIC ANIMALS

For external use only. Do not apply to cats or kittens under 8 weeks of age or weighing less than 5 lbs. As with any product, consult your veterinarian before using this product on debilitated, aged, pregnant or nursing cats. Individual sensitivities, while rare, may occur after using this pesticide product for cats. If signs persist, or become more severe, consult a veterinarian immediately. If your cat is on medication, consult your veterinarian before using this or any other product.

Side Effects: Monitor your cat after application. Side effects, although very rare, may include signs of skin irritation such as redness, scratching, or other signs of discomfort. Gastrointestinal signs such as hypersalivation, vomiting or diarrhea have also been reported. If these or other side effects (such as lethargy) occur, consult your veterinarian or call 1-800-422-9874.

For consumer questions call 1-800-255-6826.
For medical emergencies call 1-800-422-9874.

RESTRICTIONS:

- Use only on cats or kittens 8 weeks and older and weighing 5–9 lbs. Do not use on other animals.
- Do not apply more than one (1) tube per treatment.
- Do not have contact or allow children to have contact with treated area until completely dry.

DIRECTIONS FOR USE

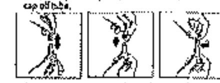
It is a violation of Federal law to use this product in a manner inconsistent with its labeling.

HOW TO OPEN

1. Being careful not to cut close to the blister cavities, take scissors and cut off one section of the card containing a single tube.
2. Take the separated section, and cut into the blister cavity across the small side, close to the cap of the tube.
3. Peel off the foil, and take out the tube.
4. Repeat steps 1 to 3 for each tube.

HOW TO APPLY

1. Remove one applicator tube from the package. See "HOW TO OPEN" section.
2. Hold applicator tube in an upright position facing away from you and your pet's face and eyes. Pull cap off tube.



3. Turn the cap around and place other end of cap back on tube.
4. Twist cap to break seal, then remove cap from tube.
5. Part the hair on the neck at the base of the skull until the skin is visible. Place the tip of the tube on the skin and squeeze the tube to expel the entire contents directly on the skin. *Do not get this product in your cat's eyes, or allow your cat to ingest this product. The product is bitter tasting and salivation may occur for a short time if the cat licks the product immediately after treatment.* Treatment at the base of the skull will minimize the opportunity for the cat to lick the product. Do not allow the product to run off.

6. Discard empty tube as described in Storage and Disposal.
7. Under normal conditions this product is effective for a month. However, in case of severe flea infestation, retreatment may be necessary earlier than four (4) weeks. Do not retreat more often than once every seven (7) days. After flea control is attained, return to a monthly retreatment schedule.

Manufactured for Bayer HealthCare LLC, Animal Health Division, P.O. Box 390, Shawnee Mission, KS 66201, USA

Bayer, the Bayer Cross and Advantage are registered trademarks of Bayer.

Made in Germany

© 2012 Bayer HealthCare LLC

09141069, R.2
EPA Est. No. 11556-DE-1
EPA Reg. No. 11556-151

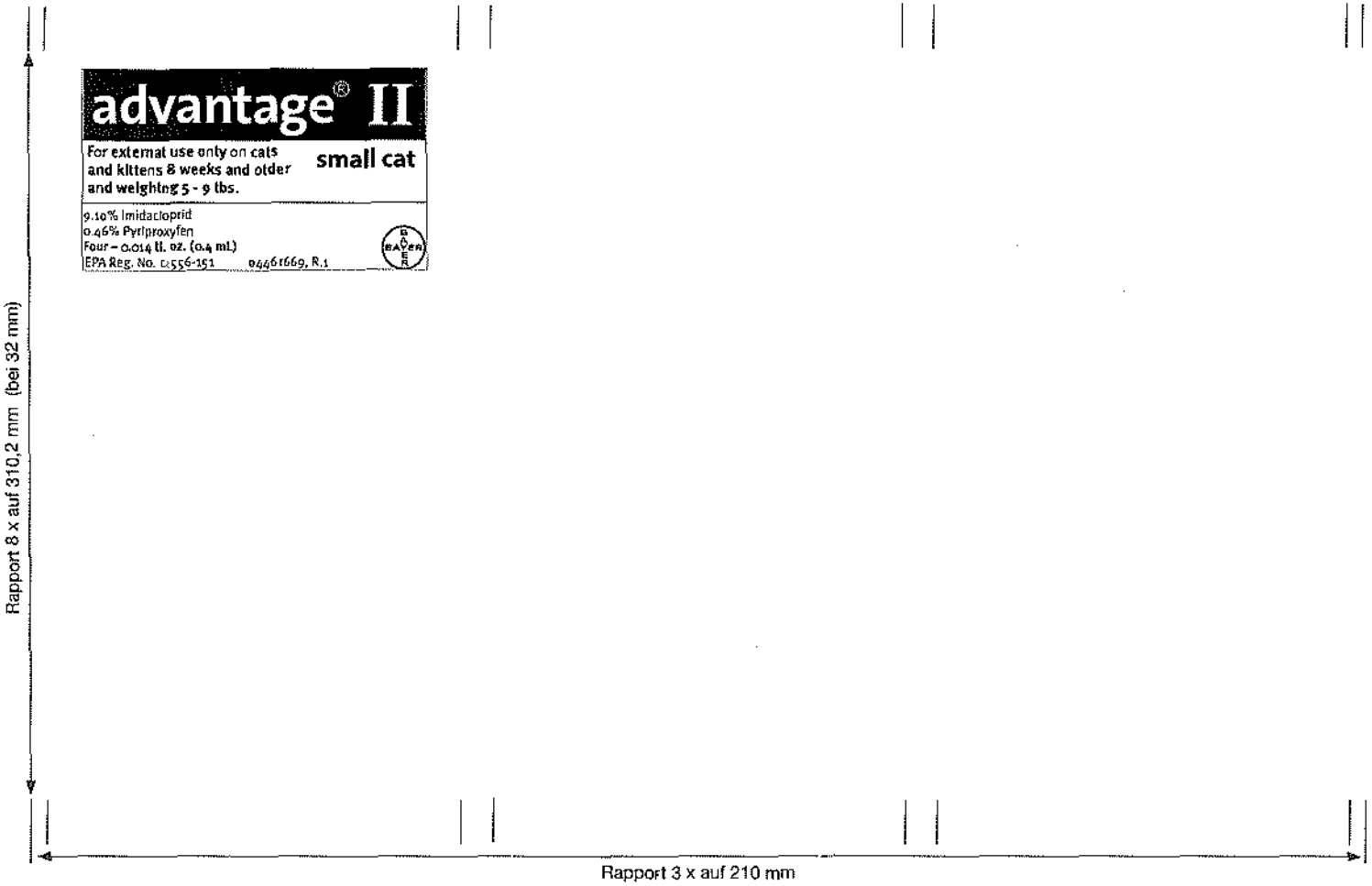
Net Contents: 4 Tubes, each 0.014 fl. oz. (0.4 ml)

Lot No.:

LSD GmbH & Co. KG, In der Steele 13, 40599 Düsseldorf, Tel. 0211-7 48 49-0, Fax -410	PM no.: 79145950 CR no.: 004736 Format: 105 x 25 x 165 mm Font size: 6.0 t Drawing no.: 5600	Bayer Animal Health GmbH approved by BAH-PS-TO/PT	In case of questions phone: +49 2173 38...
	Colours: CM K, Pantone 152, Pantone 349, Stanze — Operator ID: LR; Version no.: 6; Date: 03.08.2010	Technology on ...... by ...... Text + Layout on ...... by	technology: Thomas Fromm (VTFRT) 4102; Jörg Habig (TGHAJ) 5519; Uwe Müller (TGMUE) 4614; Otto Wilinski (VTWIE) 4703. Text + Presentation: Christina Hüter (PHUKC) 4720; Rita Fabricius Reich (VTRER) 4098; Yvonne Sabaryl (TGYVO) 4082; Renate Steinacker (VTSTE) 3046

This proof is NOT a true representation of the final colours that will be printed.

Reviewed & acceptable per spot on mitigation 10/25/12 ABM



LSD GmbH & Co. KG In der Steele 13 · 40599 Düsseldorf Tel.: 0211-7 48 49-0 · Fax.-410	PM no.: 79145942 CR no.: 004236 Format: 210 mm Font size: 6 pt Drawing no.: 9949		Bayer Animal Health GmbH approved by BAH-PS-TO/PT	In case of questions phone: +49 2173 38...
	Colours: Schwarz Stanze	Operator ID: AG Version no.: 1 Date: 20.07.2010	Technology on ..... by ..... Text + Layout on ..... by	Technology: Thomas Fromm (VTFRT)..... 4702 Jörg Habig (TGHAJ)..... 5519 Uwe Müller (TGMUE)..... 4614 Otto Wilinski (VTWIL)..... 4701 Text + Presentation: Christina Höfer (PHJNC)..... 4724 Rita Felicitas Reich (VTRER)..... 4098 Yvonne Sabatini (TGYVO)..... 4082 Renato Steinacker (VTS7E)..... 3046
This proof is NOT a true representation of the final colours that will be printed.				

advantage® II

small cat

Once-A-Month Topical Flea Prevention and Treatment for Cats
For Use ONLY on Cats 8 Weeks and Older and Weighing 5 - 9 lbs.

READ THE ENTIRE LABEL BEFORE EACH USE.

For the Prevention and Treatment of Flea Infestations
- Kills all flea life stages
- Controls existing flea infestations on your cat and prevents further infestations
- Kills fleas within 12 hours of application
- Convenient, easy-to-apply topical solution
- Fragrance-free
- Waterproof

Active Ingredients	% By Weight
Imidacloprid	9.10%
Pyriproxyfen	0.46%
Other Ingredients	90.44%
Total	100.00%

See back for First Aid and Precautionary Statements.

DIRECTIONS FOR USE

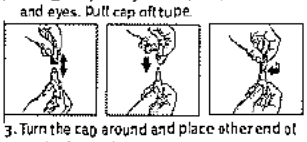
It is a violation of Federal Law to use this product in a manner inconsistent with its labeling.

HOW TO OPEN

1. Being careful not to cut close to the blister cavities, take scissors and cut off one section of the card containing a single tube.
2. Take the separated section, and cut into the blister cavity across the small side, close to the cap of the tube.
3. Peel off the foil, and take out the tube.
4. Repeat steps 1 to 3 for each tube.

HOW TO APPLY

1. Remove one applicator tube from the package. See "HOW TO OPEN" section.
2. Hold applicator tube in an upright position facing away from you and your pet's face and eyes. Pull cap off tube.



3. Turn the cap around and place other end of cap back on tube.
4. Twist cap to break seal, then remove cap from tube.
5. Part the hair on the neck at the base of the skull until the skin is visible. Place the tip of the tube on the skin and squeeze the tube to expel the entire contents directly on the skin. *Do not get this product in your cat's eyes, or allow your cat to ingest this product. The product is bitter tasting and salivation may occur for a short time if the cat licks the product immediately after treatment.* Treatment at the base of the skull will minimize the opportunity for the cat to lick the product. Do not allow the product to run off.

6. Discard empty tube as described in Storage and Disposal.
7. Under normal conditions this product is effective for a month. However, in case of severe flea infestation, retreatment may be necessary earlier than four (4) weeks. Do not retreat more often than once every seven (7) days. After flea control is attained, return to a monthly retreatment schedule.

PRODUCT INFORMATION

The successive feeding activity of fleas on cats frequently elicits a hypersensitivity skin disorder known as flea allergy dermatitis (FAD) or flea bite hypersensitivity. Treatment of cats with Advantage II Small Cat kills fleas and reduces the incidence of this condition.

Advantage II Small Cat kills the existing fleas on cats within 12 hours. Reinfesting fleas are killed within 2 hours with protection against further flea infestation lasting for up to four (4) weeks. Pre-existing pupae in the environment may continue to emerge for six (6) weeks or longer depending upon the climatic conditions.

Fleas, eggs and larvae in the cat's surroundings are killed following contact with an Advantage II Small Cat treated cat. Advantage II Small Cat provides multi-stage flea control effectively breaking all flea life-cycle stages for lasting control of flea populations.

Advantage II Small Cat kills adult fleas quickly, within 12 hours, inhibits the development of immature flea life stages and prevents them from reaching the biting adult stage.

Advantage II Small Cat is waterproof and remains effective following a shampoo treatment or after exposure to rain or sunlight.

Apply monthly treatments for optimal control and prevention of fleas.

LSD GmbH & Co. KG
In der Steele 13 · 40599 Düsseldorf
Tel.: (0211) 748 49-0 · Fax: 410

PM no.: T0t13660
CR no.: 004236/004237
Format: 148 x 297 mm
Font size: 9 pt
Drawing no.:

Colours: Schwarz Stanze
Operator ID: LR
Version no.: 8
Date: 03.08.2010

Bayer Animal Health GmbH
approved by BAH-PS-TD/PT
Technology
on .....
by .....
Text + Layout
on .....
by .....

In case of questions phone: +49 2173 38...
Technology:
Thomas Tramm (VTFRT) 4702
Jörg Hasig (TGHAJ) 6519
Uwe Müller (TGMUE) 4914
Otto Yilkinski (VTWIL) 4701
Text + Presentation:
Christina Höfer (PHJNC) 4724
Rita Tsiplakis Treich (VTRTR) 4096
Yvonne Sabatini (TGYVO) 4082
Renate Steinacker (VTSTE) 3048

This proof is NOT a true representation of the final colours that will be printed.

Advantage II - Cat products (11556-150, -151, and -152)
Doug Spilker
to:
Autumn Metzger
10/10/2012 09:12 AM
Cc:
Venus Eagle
Hide Details
From: Doug Spilker <doug.spilker@bayer.com>

To: Autumn Metzger/DC/USEPA/US@EPA

Cc: Venus Eagle/DC/USEPA/US@EPA

History: This message has been replied to.

6 Attachments


Advantage II Kitten jb highlighted.pdf

Advantage II Kitten jb.pdf

Advantage II Large Cat jb highlighted.pdf

Advantage II Large Cat jb.pdf

Advantage II Small Cat jb highlighted.pdf

Advantage II Small Cat jb.pdf

Hi Autumn,
Please find attached the draft master labels (1 clean copy; 1 highlighted copy), text dated 9/25/2012, for the Advantage II Kitten (11556-150), Advantage II Small Cat (11556-151) and Advantage II Large Cat (11SS6-152). The following are the text changes that were made from the last version. All of the elements of the Final Printed Labeling (facsimile) for these products will be sent under separate emails by product.

Page	Changes to Master label
Page 1	Updated text date to 9/25/12; updated version designation from "ja" to "jb" – see file name.
Page 1	Changed referral statement to show that First Aid appears inside on insert. This was agreed to in email of 8/24/12 (A. Metzger to D. Spilker).

Page 2	First Aid removed, and moved to page 6 (insert).
Page 6-7	Added First Aid section and ***duplicated*** Precautionary Statements, Hazards et al. (from page 2) so that it will match the insert of the Final printed labeling.

Please call if you have questions or the labels do not come through correctly.

Best Regards,
Doug

Douglas A. Spilker, Ph.D.
Manager - EPA Reg. Affairs
BAYER HEALTHCARE LLC
Animal Health Division
Office: 913-268-2751
Mobile: 816-506-3102
Email: doug.spilker@bayer.com

Address:
P.O. Box 390
Shawnee Mission, KS 66201-0390
Country: USA

Bayer Animal Health "Protecting.Curing.Caring...Together"

RE: Advantage II Cat Labels (11556-150, -151 and -152)
Doug Spilker to: Autumn Metzger 09/24/2012 12:51 PM

History: This message has been replied to.

Thanks. I never got any stamped labels!?

However, will do. Do I send via email or through the mailroom?

Best Regards,
Doug

Douglas A. Spilker, Ph.D.
Manager - EPA Reg. Affairs
BAYER HEALTHCARE LLC
Animal Health Division
Office: 913-268-2751
Mobile: 816-506-3102
Email: doug.spilker@bayer.com

Address:
P.O. Box 390
Shawnee Mission, KS 66201-0390
Country: USA

Bayer Animal Health "Protecting.Curing.Caring...Together"

From: Autumn Metzger [mailto:Metzger.Autumn@epamail.epa.gov]
Sent: Monday, September 24, 2012 11:48 AM
To: Doug Spilker
Cc: Angela Mall; Venus Eagle
Subject: RE: Advantage II Cat Labels (11556-150, -151 and -152)

Hi Doug,

This is precisely the reason we are asking for the final printed labels. These things have to be worked out to ensure they all fit and match what we stamp. So yes, what you propose is fine, however now we need to start the process over and re-stamp labels. Please re-submit these with no other changes and a very clear cover letter.

Autumn Metzger
Biologist
U.S. Environmental Protection Agency
Insecticide-Rodenticide Branch
Registration Division (7S05P)
1200 Pennsylvania Ave. NW
Washington, DC 20460

Tel: 703 305-5314
Fax: 703 308-5433
Email: metzger.autumn@epa.gov

-----Doug Spilker <doug.spilker@bayer.com> wrote: -----
To: Autumn Metzger/DC/USEPA/US@EPA
From: Doug Spilker <doug.spilker@bayer.com>
Date: 09/24/2012 11:24AM
Cc: Angela Mall <angela.strauss@bayer.com>, Venus Eagle/DC/USEPA/US@EPA
Subject: RE: Advantage II Cat Labels (11556-150, -151 and -152)
Good Morning Autumn,

They are working on these package labels to try and meet your deadline. However, they are having trouble fitting all of the new information on the back panel – e.g. new Restrictions section, side effects et al. We would like your permission to move the First Aid section to the insert (and of course change the referral statement to reflect this.) The Precautionary Statements (Hazard to Humans, Hazard to Domestic Animals, Side Effects, and Restrictions would appear on the back panel.) ALL of this information would also be repeated in its entirety on the insert, so the insert is very complete – including all the proper positioning of the First Aid statements with the Precautionary statements.

As I read the LRM (7-10), it says that the Agency may permit reasonable variations in placement of the First Aid statements as long as the referral statement appears on the front panel. We feel this is a reasonable request, and does not increase any potential hazard in using the product.

We ask for your permission to do this. If you need revised Master labels to reflect this change, please let me know and we will fix it.

Best Regards,
Doug

Douglas A. Spilker, Ph.D.
Manager - EPA Reg. Affairs
BAYER HEALTHCARE LLC
Animal Health Division
Office: 913-268-2751
Mobile: 816-506-3102
Email: doug.spilker@bayer.com

Address:
P.O. Box 390
Shawnee Mission, KS 66201-0390
Country: USA

Bayer Animal Health "Protecting.Curing.Caring...Together"

From: Autumn Metzger [mailto:Metzger.Autumn@epamail.epa.gov]
Sent: Tuesday, September 18, 2012 2:03 PM
To: Doug Spilker
Subject: Re: Advantage II Cat Labels (11556-150, -151 and -152)

Hi Doug,

These all look ok. Please go ahead and use these to update the final printed labeling for each and submit

to me via email (if possible). We cannot close lhese out without that part (since I have to be sure the font sizes/colors/pictures and everylhing else are adequately translated lo the final printed labeling). Can we shoot for lhis back to me within 3 weeks? We'll have to have this closed out before we can finish up the ferret amendment and we would rather not push that back.

Autumn Metzger
Biologist
U.S. Environmental Protection Agency
Insecticide-Rodenticide Branch
Registration Division (7505P)
1200 Pennsylvania Ave. NW
Washington, DC 20460

Tel: 703 305-5314
Fax: 703 308-5433
Email: metzger.autumn@epa.gov

Doug Spilker ---09/07/2012 07:47:47 AM---Hi Autumn, Here's your welcome back present. Attached are the revised labels for the cat products wi

From: Doug Spilker <doug.spilker@bayer.com>
To: Autumn Metzger/DC/USEPA/US@EPA
Cc: Venus Eagle/DC/USEPA/US@EPA
Date: 09/07/2012 07:47 AM
Subject: Advantage II Cat Labels (t t556-150, -151 and -152)

Hi Autumn,
Here's your welcome back present. Attached are the revised labels for the cat products with the changes you requested. I have looked at these ad nauseam, and I hope I fixed everything. The Advantage II dog labels will be in a separate email. I am in the office next week on Monday, and Friday, but in DC Tuesday thru Thursday. I'm hoping we don't, but let me know if we need to work on these some more.

Best Regards,
Doug

Douglas A. Spilker, Ph.D.
Manager - EPA Reg. Affairs
BAYER HEALTHCARE LLC
Animal Health Division
Office: 913-268-2751
Mobile: 816-506-3102
Email: doug.spilker@bayer.com

Address:
P.O. Box 390
Shawnee Mission, KS 66201-0390
Country: USA

Bayer Animal Health "Protecting.Curing.Caring...Together"

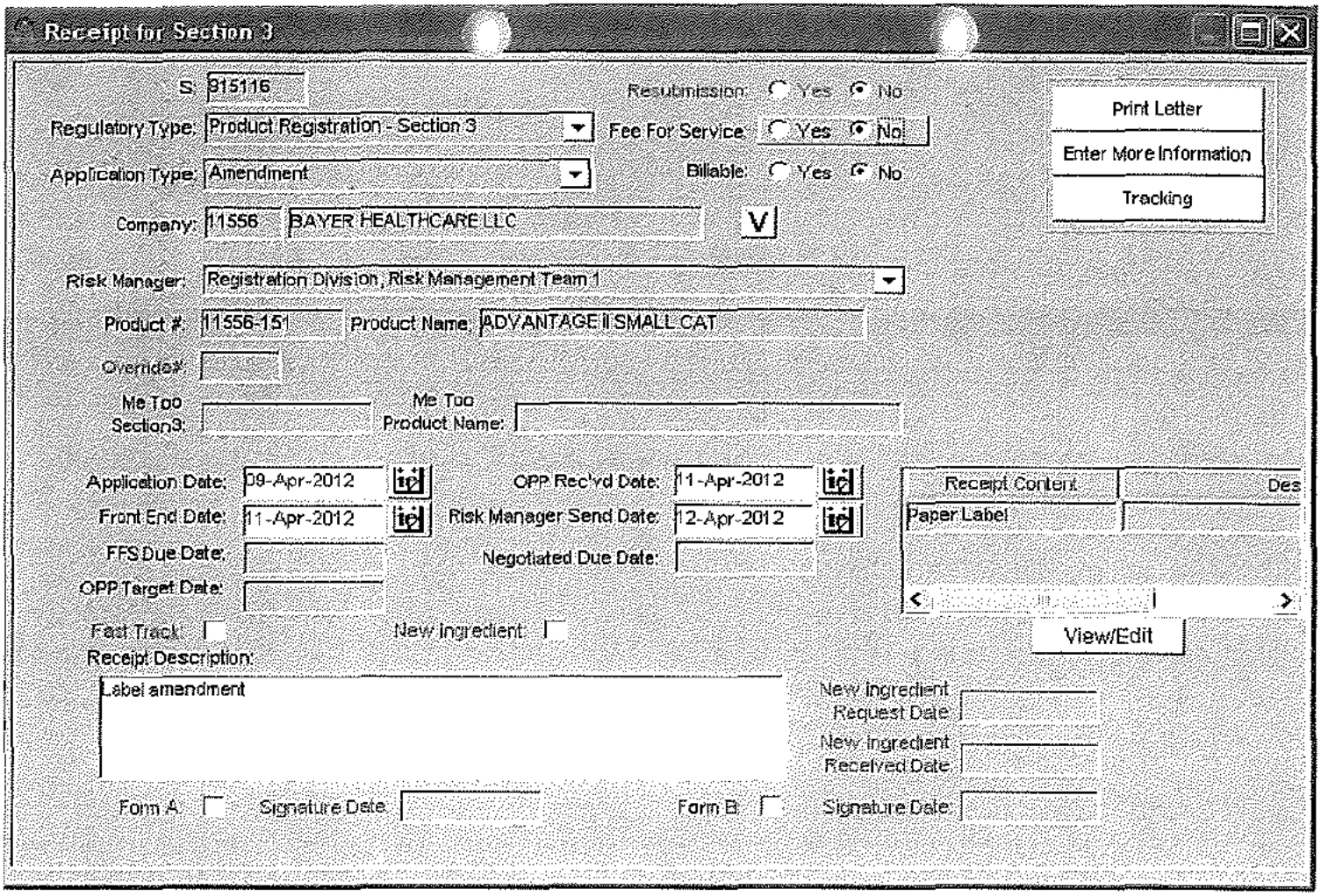
(See attached file: Advantage II Kitten ja.pdf)(See attached file: Advantage II Small Cat ja.pdf)(See attached file: Advantage II Large Cat ja.pdf)

FAST-TRACK AMENDMENTS – Completeness Screening Checklist

Expert's In-Processing Signature: _____ Date: 4/17/12 PM #: 1

EPA Reg. Number: 11556-151	EPA Receipt Date:

	Checklist Item	Yes	No	N/A
1	**Application Form** (EPA Form 8570-1) - signed?	✓		
2	**Confidential Statement of Formula** (EPA Form 8570-29) - signed?			✓
3	**Certification with Respect to Citation of Data** (EPA Form 8570-34) - signed?			✓
4	**Formulator's Exemption Statement** (EPA Form 8570-27) - signed?			✓
5	**Data Matrix** (EPA Form 8570-35) [Applicable for adding me-too uses] - signed?			✓
	a) Selective Method?			
	b) Cite-All Method?			
	c) Public copy of Matrix provided? See PR Notice 98-5			
6	**Is Label included?** (5 copies)	✓		
	a) Electronic Label available?			
	Comments:			


Receipt for Section 3
S 815116
Resubmission: Yes No
Regulatory Type: Product Registration - Section 3
Fee For Service: Yes No
Application Type: Amendment
Billable: Yes No
Company: 11556 BAYER HEALTHCARE LLC
Print Letter
Enter More Information
Tracking
Risk Manager: Registration Division ; Risk Management Team 1
Product #: 11556-151
Product Name: ADVANTAGE II SMALL CAT
Override?:
Me Too Section3:
Me Too Product Name:
Application Date: 09-Apr-2012
OPP Rec'vd Date: 11-Apr-2012
Front End Date: 11-Apr-2012
Risk Manager Send Date: 12-Apr-2012
FFS Due Date:
Negotiated Due Date:
OPP Target Date:
Receipt Content
Des
Paper Label
Fast Track:
New Ingredient:
View/Edit
Receipt Description:
Label amendment
New Ingredient Request Date:
New Ingredient Received Date:
Form A:
Signature Date:
Form B:
Signature Date:

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

April 12, 2012

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DR. BRUCE MARTIN
BAYER HEALTHCARE LLC
ANIMAL HEALTH DIVISION
PO Box 390
SHAWNEE MISSION, KS 66201-0390

PRODUCT NAME: ADVANTAGE II SMALL CAT
COMPANY NAME: BAYER HEALTHCARE LLC
OPP IDENTIFICATION NUMBER:
EPA FILE SYMBOL: 11556-151
EPA RECEIPT DATE: 04/11/12

SUBJECT: RECEIPT OF AMENDMENT

DEAR REGISTRANT:

The Office of Pesticide Programs has received your application for an amendment and it has passed an administrative screen for completeness.

During the initial screen we determined that the application appears to qualify for fast track review. The package will now be forwarded to the Product Manager for review to determine its acceptability for fast track status.

If you have any questions, please contact Registration Division, Risk Management Team 1, at (703) 308-8045.

Sincerely,

Front End Processing Staff
Information Services Branch
Information Technology & Resources Management Division

Fee for Service {915116É~

This package includes the following

- ○ New Registration
- ◉ Amendment

☐ Studies? ☐ Fee Waiver?

☐ volpay % Reduction: ___

for Division

- ○ AD
- ○ BPPD
- ◉ RD

Risk Mgr. 1

Receipt No. S- 915116

EPA File Symbol/Reg. No. 11556-151

Pin-Punch Date: 4/11/2012

☒ This item is NOT subject to FFS action.

Action Code:

Requested:

Granted:

Amount Due: $ _____

Parent/Child Decisions:

☐ Inert Cleared for Intended Use ☐ Uncleared Inert in Product

Reviewer: [signature] Date: 4/12/12

Remarks:

Bayer HealthCare
Animal Health

Via Federal Express

April 9, 2012

Document Processing Desk (AMEND- Pet Spot-on)
Office of Pesticide Programs (7505P)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Attention: Ms. Venus Eagle/PM 01

Subject: Advantage II Kitten (EPA Reg. No. 11556-150)
Advantage II Small Cat (EPA Reg. No. 11556-151)
Advantage II Large Cat (EPA Reg. No. 11556-152)

Bayer HealthCare LLC
Animal Health
P.O. Box 390
Shawnee Mission, KS 66201-0390

Dear Ms. Eagle:

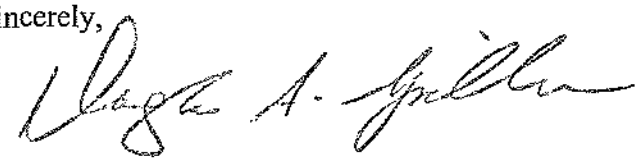
Reference is made to the current registrations of the subject products, and the Agency's letter to us, dated September 20, 2011 (received October 11, 2011), regarding "Implementation of Label Changes to Pet Spot-on Products."

Please find enclosed for the Agency's review and acceptance respective applications and revised draft labeling, dated 03/26/2012, for each of the subject dog spot-on products. Many of the revisions are in response to the aforementioned EPA "Implementation" letter, but we have also taken the opportunity in these amendments to make a few minor word and format changes. However, there have been no revisions of any efficacy claims.

The letter from the Agency requests the submission of "packaging" of these products. In addition to the enclosed "Master" labels for the products, we have also enclosed one copy of the printer's proofs of each element of the Final Printed Labeling (packaging) for these products.

Since the mandated label revisions outlined in the aforementioned Agency letter affect all pet spot-on pet registrations, we encourage the Agency to issue a PR Notice, or other regulatory document, that will also mandate a single date of packaging compliance for the entire affected industry as one. If you have any questions, please do not hesitate to call (913-268-2751).

Sincerely,



Douglas A. Spilker. Ph. D.
Manager, EPA Regulatory Affairs
Doug.Spilker@Bayer.com

Enclosures:

1) Advanatge II Kitten - Application w/att.
2) Advantage II Kitten - Draft label, dated 3/26/12 (3 copies)
3) Advantage II Kitten - Final printed labeling proofs (1 copy)
4) Advanatge II Small Cat - Application w/att.
5) Advantage II Small Cat - Draft label, dated 3/26/12 (3 copies)
6) Advantage II Small Cat - Final printed labeling proofs (1 copy)
7) Advanatge II Large Cat - Application w/att.
8) Advantage II Large Cat - Draft label, dated 3/26/12 (3 copies)
9) Advantage II Large Cat - Final printed labeling proofs (1 copy)

Please read instructions on reverse before completing form. Form Approved, OMB No. 2070-0060

EPA

United States
Environmental Protection Agency
Washington, DC 20460

☐ **Registration**
☒ **Amendment**
☐ **Other:**

OPP Identifier Number

Application for Pesticide - Section I

1. Company/Product Number	2. EPA Product Manager	3. Proposed Classification
11556-151	**Venus Eagle**	☒ None ☐ Restricted
4. Company/Product (Name) **Advantage II Small Cat**	PM# **1**	
5. Name and Address of Applicant *(Include ZIP Code)* **Bayer HealthCare LLC, Animal Health Division PO Box 390 Shawnee Mission, KS 66201** ☐ *Check if this is a new address*	6. **Expedited Review.** In accordance with FIFRA Section 3(c)(3)(b)(I), my product is similar or identical in composition and labeling to: EPA Reg. No. _____ Product Name _____	

Section - II

☒ Amendment – Explain below.
☐ Resubmission in response to Agency letter dated _____
☐ Notification - Explain below.
☐ Final printed labels in response to Agency letter dated _____
☐ "Me Too" Application
☐ Other - Explain below

Explanation:
NON-PRIA ACTION (AMEND – Pet Spot-on). See attached for more detail.
Enclosed for Agency acceptance is revised draft labeling for the subject product, dated 03/26/12. Revisions include those in response to the EPA "Implementation of Label Changes to Pet Spot-On Products" document, dated 9/30/11 (Received 10/11/11), and other minor word and format changes. Final Printed Labeling for this product is also enclosed.

Section - III

1. Material This Product Will Be Packaged In:

Child-Resistant Packaging	Unit Packaging	Water Soluble Packaging	2. Type of Container
☐ Yes* ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Metal ☐ Plastic ☐ Glass ☐ Paper ☐ Other (Specify)
***Certification must be submitted**	If "Yes" Unit Packaging wgt. / No. per container	If "Yes" Package wgt. / No. per container	

3. Location of Net Contents Information	4. Size(s) Retail Container	5. Location of Label Directions
☐ Label ☐ Container		☐ On Label ☐ On labeling accompanying product

6. Manner in Which Label is Affixed to Product ☐ Lithograph ☐ Paper glued ☐ Stenciled ☐ Other _____

Section - IV

1. Contact Point *(Complete items directly below for identification of individual to be contacted, if necessary, to process this application)*

Name	Title	Telephone No. (Include Area Code)
Douglas A. Spilker, Ph.D.	Manager, EPA Regulatory Affairs	913-268-2751

Certification

I certify that the statements I have made on this form and all attachments thereto are true, accurate and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine or imprisonment or both under applicable law.

2. Signature	3. Title	6. Date Application Received (Stamped)
Douglas A. Spilker	Manager, EPA Regulatory Affairs	
4. Typed Name Douglas A. Spilker, Ph.D. (doug.spilker@bayer.com)	5. Date 9 April 2012	

EPA Form 8570-1 (Rev. 8-94) Previous editions are obsolete — White- EPA File Copy (original) Yellow- Applicant Copy

ATTACHMENT FOR
APPLICATION FOR PESTICIDE REGISTRATION
April 5, 2012

Advantage II Small Cat (EPA Reg. No. 11556-151)

Please find enclosed for the Agency's review and acceptance revised draft labeling, dated 03/26/12, for the subject product. Many of the revisions are in response to the EPA "Implementation of Label Changes to Pet Spot-On Products" document, dated 9/30/11 (Received 10/11/11), but we have also taken the opportunity in this amendment to make a few minor word and format changes. However, there have been no revisions of any efficacy claims. Also, enclosed is the Final Printed Labeling for this product, as requested in the aforementioned EPA document.

The proposed changes to the draft labeling are:

Page 1:

1. Revision of the weight and age restriction statement, with a box surrounding it.
2. Slight revision of the referral statements.

Page 2:

3. Addition of "Side Effects" text in a box; basically the "boiler plate" language specified by the Agency in the aforementioned document, with slight product-specific modifications, based on the findings in the EPA-accepted Companion Animal Safety studies for this product, and from accident reports from cases of properly applied product.
4. Addition of 1-800 numbers for carton.

Page 3:

- No changes.
-

Page 4:

5. Incorporation of the required "do not allow your cat to ingest this product" statement into the language of the bullet #6 of the draft label.

Pages 5-9:

- No changes.

No other substantive changes have been made to this label, except for those listed above. Therefore, we hope that these minor changes to the label can be readily accepted by the Agency for this product, as well as, for the revised label of the other Advantage cat products – Advantage II Kitten & Advantage II Large Cat - submitted concurrently with this application.

If there are any questions regarding these revisions, please contact us immediately [doug.spilker@bayer.com ; (913)-268-2751].

Material Sent for Data Extraction

Reg. # 11554 - 151

Description: _____

☐ Material(s) Sent to Data Extraction Contractors:

- ☑ New Stamped Label Dated 11/8/12
- ☐ Notification Dated _____
- ☐ New CSF(s) Dated _____
- ☐ Other: _____

☐ Decision #: _____

☐ Other Action/Comments: _____

_____

File this coversheet and attached materials in the jacket. It must be well organized and clipped together, NOT STAPLED. Then give the jacket with the coversheet and materials to staff in the Information Services Center (ISC) (Room S-4900). If a jacket is full or only available as an image, please file materials in a new jacket and bring it down to the (ISC). For further information please call 703-605-0716.

Reviewer: Autumn Metzger

Phone: 305-5314 Division: RD - IRB

Date: 11/8/12

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

NOV 0 8 2012

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

Douglas Spilker, Ph.D
Bayer HealthCare LLC, Animal Health Division
P.O. Box 390
Shawnee Mission, KS 66201-0390

Dear Dr. Spilker:

Subject: PRIA Amendment add flea control against Ferrets to label
EPA Registration No: 11556-151
Product name: Advantage II Small Cat
Decision Number: 466880

The labeling referred to above submitted in connection with the Federal Insecticide, Fungicide and Rodenticide, as amended are acceptable.

As a reminder, this **registration is time-limited and expires January 17, 2013**. You must apply to extend the expiration and/or to change the terms of this registration.

A stamped copy of the labeling is enclosed for your records. If you have any questions regarding this label, please contact Autumn Metzger at (703) 305-5314.

Sincerely,

Venus Eagle
Product Manager 01
Insecticide-Rodenticide Branch
Registration Division (7505P)

Reason To Issue: To add new use on ferrets. Date: 11/07/12
Supersedes: 09/25/12

NOTE TO REVIEWER: [(Brackets and parentheses indicate alternate language)]

[Front Panel]

Advantage® II Small Cat

Once-A-Month Topical Flea Prevention and Treatment for Cats and Ferrets
For Use ONLY on Cats 8 Weeks and Older and Weighing 5 - 9 lbs. or Ferrets 10 weeks and Older and Weighing 1 lb. or Greater

[Selected optional claims bulleted here from page 11 and/or 12]

-
-
-
-

Active Ingredients	% By Weight
Imidacloprid	9.10%
Pyriproxyfen	0.46%
Other Ingredients	90.44%
Total	100.00%

EPA Est. No. 11556-XXX-X EPA Reg No. 11556-151

KEEP OUT OF REACH OF CHILDREN

CAUTION

See back panel for Precautionary Statements.
For Directions for Use, Storage and Disposal, and First Aid see package insert inside.

ACCEPTED
NOV 0 8 2012
Under the Federal Insecticide, Fungicide, and Rodenticide Act, as amended, for the pesticide registered under:
EPA. Reg. No: 11556-151

[Back Panel]

Advantage® II Small Cat

Once-A-Month Topical Flea Prevention and Treatment for Cats and Ferrets
For Use ONLY on Cats 8 Weeks and Older and Weighing 5 - 9 lbs. or
Ferrets 10 weeks and Older and Weighing 1 lb. or Greater

READ THE ENTIRE LABEL BEFORE EACH USE
For the Prevention and Treatment of Flea Infestations

PRECAUTIONARY STATEMENTS
HAZARDS TO HUMANS

CAUTION: Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling. Keep out of reach of children. Do not contaminate feed or food.

HAZARDS TO DOMESTIC ANIMALS

For external use only. Do not apply to cats or kittens under 8 weeks of age or weighing less than 5 lbs. or on kits (young ferrets) under 10 weeks of age or weighing less than 1 lb. As with any product, consult your veterinarian before using this product on debilitated, aged, pregnant or nursing cats [or ferrets. Individual sensitivities, while rare, may occur after using ANY pesticide product for cats or ferrets. If signs persist, or become more severe, consult a veterinarian immediately. If your cat or ferret is on medication, consult your veterinarian before using this or any other product.

Side Effects (Cats): Monitor your cat after application. Side effects, although very rare, may include signs of skin irritation such as redness, scratching, or other signs of discomfort. Gastrointestinal signs such as hypersalivation, vomiting or diarrhea have also been reported. If these or other side effects (such as lethargy) occur, consult your veterinarian or call 1-800-422-9874.
Side Effects (Ferrets): Monitor your ferret after application. Side effects, although very rare, may include temporary changes in fecal consistency. If these or other side effects occur, consult your veterinarian or call 1-800-422-9874.

For consumer questions call 1-800-255-6826.
For medical emergencies call 1-800-422-9874.

RESTRICTIONS:

- Use only on cats or kittens 8 weeks and older and weighing 5 – 9 lbs. and only on ferrets 10 weeks and older and weighing 1 lb. or greater. Do not use on other animals.
- Do not apply more than one (1) tube per treatment.

- Do not have contact or allow children to have contact with treated area until completely dry.

Net Contents: [X] Tube(s), each 0.014 fl. oz. (0.4 mL)

[Sample - Not for (Re)Sale]

Manufactured For

Bayer HealthCare LLC
Animal Health Division
P.O. BOX 390
Shawnee Mission, Kansas 66201 USA

Made in Germany

[Back Panel and/or Insert]

Advantage® II Small Cat

Once-A-Month Topical Flea Prevention and Treatment for Cats and Ferrets
For Use ONLY on Cats 8 Weeks and Older and Weighing 5 - 9 lbs. or
Ferrets 10 weeks and Older and Weighing 1 lb. or Greater

READ THE ENTIRE LABEL BEFORE EACH USE
For the Prevention and Treatment of Flea Infestations

DIRECTIONS FOR USE

It is a violation of Federal Law to use this product in a manner inconsistent with its labeling.

HOW TO OPEN

1. Being careful not to cut close to the blister cavities, take scissors and cut off one section of the card containing a single tube.
2. Take the separated section, and cut into the blister cavity across the small side, close to the cap of the tube.
3. Peel off the foil, and take out the tube.
4. Repeat steps 1 to 3 for each tube.

HOW TO APPLY

1. Remove one applicator tube from the package. See "HOW TO OPEN" section.

2. Hold applicator tube in an upright position facing away from you and your pet's face and eyes. Pull cap off tube.

[Visuals Depicting How to Open Applicator Tube]

3. Turn the cap around and place other end of cap back on tube.

4. Twist cap to break seal, then remove cap from tube.

5. Part the hair on the neck at the base of the skull until the skin is visible. Place the tip of the tube on the skin and squeeze the tube to expel the entire contents directly on the skin. *Do not get this product in your pet's eyes, or allow your pet to ingest this*

product. The product is bitter tasting and salivation may occur for a short time if the pet licks the product immediately after treatment. Treatment at the base of the skull will minimize the opportunity for the cat to lick the product. Do not allow the product to run off.

[2 Separate Visuals (1 cat; 1 ferret) depicting Application to the Animals]

6. Discard empty tube as described in Storage and Disposal.

7. Under normal conditions this product is effective for a month. However, in case of severe flea infestation, retreatment may be necessary earlier than four (4) weeks. On cats, do not retreat more often than once every seven (7) days. On ferrets, do not retreat more often than every 14 days. After flea control is attained, return to a monthly retreatment schedule.

PRODUCT INFORMATION FOR CATS

The successive feeding activity of fleas on cats frequently elicits a hypersensitivity skin disorder known as flea allergy dermatitis (FAD) or flea bite hypersensitivity. Treatment of cats with Advantage® II Small Cat kills fleas and may reduce the incidence of this condition.

Advantage® II Small Cat kills the existing fleas on cats within 12 hours. Reinfesting fleas are killed within 2 hours with protection against further flea infestation lasting for up to four (4) weeks. Pre-existing pupae in the environment may continue to emerge for six (6) weeks or longer depending upon the climatic conditions.

Fleas, eggs and larvae in the cat's surroundings are killed following contact with an Advantage® II Small Cat treated cat. Advantage® II Small Cat provides multi-stage flea control effectively breaking all flea life-cycle stages for lasting control of flea populations.

Advantage® II Small Cat kills adult fleas quickly, within 12 hours, inhibits the development of immature flea life stages and prevents them from reaching the biting adult stage.

Advantage® II Small Cat is waterproof and remains effective following a shampoo treatment or after exposure to rain or sunlight.

Apply monthly treatments for optimal control and prevention of fleas.

PRODUCT INFORMATION FOR FERRETS

Advantage® II Small Cat kills the existing fleas on ferrets within 24 hours. Reinfesting fleas are killed with protection against further flea infestation lasting for up to four (4) weeks. Pre-existing pupae in the environment may continue to emerge for six (6) weeks or longer depending upon the climatic conditions.

Fleas, eggs and larvae in the ferret's surroundings are killed following contact with an Advantage® II Small Cat treated ferret. Advantage® II Small Cat provides multi-stage flea control effectively breaking all flea life cycle stages for lasting control of flea populations.

Advantage® II Small Cat kills adult fleas within 24 hours, inhibits the development of immature flea life stages and prevents them from reaching the biting adult stage.

Advantage® II Small Cat is waterproof and remains effective following a shampoo treatment or after exposure to rain or sunlight.

Apply monthly treatments for optimal control and prevention of fleas.

KEEP OUT OF REACH OF CHILDREN

CAUTION

PRECAUTIONARY STATEMENTS
HAZARDS TO HUMANS

CAUTION: Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling. Keep out of reach of children. Do not contaminate feed or food.

FIRST AID	
If Swallowed:	• Call a poison control center or doctor immediately for treatment advice. • Have person sip a glass of water if able to swallow. • Do not induce vomiting unless told to do so by the poison control center or doctor. • Do not give anything to an unconscious person.
If In Eyes:	• Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. • Call a poison control center or doctor for treatment advice.
If On Skin	• Wash with plenty of soap and water.
HOT LINE NUMBER	
Have the product container or label with you when calling a poison control center or doctor, or going for treatment. For medical emergencies call 1-800-422-9874. For customer questions call 1-800-255-6826.	
NOTE TO PHYSICIAN	
Treat the patient symptomatically.	

HAZARDS TO DOMESTIC ANIMALS

For external use only. Do not apply to cats or kittens under 8 weeks of age or weighing less than 5 lbs. or on kits (young ferrets) under 10 weeks of age or weighing less than 1 lb. As with any product, consult your veterinarian before using this product on debilitated, aged, pregnant or nursing cats or ferrets. Individual sensitivities, while rare, may occur after using ANY pesticide product for cats or ferrets. If signs persist, or become more severe, consult a veterinarian immediately. If your cat or ferret is on medication, consult your veterinarian before using this or any other product.

Side Effects (Cats): Monitor your cat after application. Side effects, although very rare, may include signs of skin irritation such as redness, scratching, or other signs of discomfort. Gastrointestinal signs such as hypersalivation, vomiting or diarrhea have also been reported. If these or other side effects (such as lethargy) occur, consult your veterinarian or call 1-800-422-9874.
Side Effects (Ferrets): Monitor your ferret after application. Side effects, although very rare, may include temporary changes in fecal consistency. If these or other side effects occur, consult your veterinarian or call 1-800-422-9874.

For consumer questions call 1-800-255-6826.
For medical emergencies call 1-800-422-9874.

RESTRICTIONS:

- Use only on cats or kittens 8 weeks and older and weighing 5 – 9 lbs. and only on ferrets 10 weeks and older and weighing 1 lb. or greater. Do not use on other animals.
- Do not apply more than one (1) tube per treatment.
- Do not have contact or allow children to have contact with treated area until completely dry.

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal.

Pesticide Storage: Store in a cool, dry place inaccessible to children and pets. **Pesticide Disposal and Container Handling:** Nonrefillable container. **If empty:** Do not reuse or refill this container. Place in trash or offer for recycling if available. **If partly filled:** Call your local solid waste agency or 1-800-422-9874 for disposal instructions. Never place unused product down any indoor or outdoor drain.

LIMITED WARRANTY AND LIMITATION OF DAMAGES

Bayer HealthCare LLC, Animal Health Division warrants that this material conforms to the chemical description on the label. TO THE EXTENT CONSISTENT WITH APPLICABLE LAW, BAYER MAKES NO OTHER EXPRESS OR IMPLIED WARRANTY, INCLUDING ANY OTHER EXPRESS OR IMPLIED WARRANTY OF FITNESS OR MERCHANTABILITY, and no agent of Bayer is authorized to do so except in writing with a specific reference to this warranty. Any damages arising from a breach of this warranty shall be limited to direct damages and shall not include consequential commercial damages such as loss of profits or values, etc.

[Label on Individual Tube]

Advantage® II Small Cat

9.10% Imidacloprid

0.46% Pyriproxyfen

0.014 fl. oz. (0.4 mL)

EPA Reg. No. 11556-151

Keep Out of Reach of Children

CAUTION

Read The Entire Label Before Use

BAYER

Lot No. 0000000

[Label on blister card; one card containing 1, 2, 3, 4, 5, or 6 tubes]

Advantage® II Small Cat

For external use only on cats and kittens 8 weeks and older and weighing 5 - 9 lbs.
or ferrets 10 weeks and older and weighing 1 lb. or greater

9.10% Imidacloprid

0.46% Pyriproxyfen

[X] - 0.014 fl. oz. (0.4 mL)

EPA Reg. No. 11556-151

BAYER

NOTE TO REVIEWER: [(Brackets and parentheses indicate alternate language)]

OPTIONAL MARKETING CLAIMS [Appearing on any panel]

- For use on cats and kittens 8 weeks of age and older
- For use on ferrets and (and kits) 10 weeks of age and older
- Advantage II contains [imidacloprid], [and an/the] [insect growth regulator] [IGR] [pyriproxyfen]
- A single topical application remains effective for up to [4 weeks] [a month]
- Convenient, easy-to-apply topical solution
- Convenient, easy-to-apply and fragrance free [monthly] [topical solution]
- Once a month topical flea prevention and treatment for cats 8 weeks of age or older [and ferrets 10 weeks of age and older]
- Advantage II is indicated for the prevention and treatment of fleas on cats 8 weeks of age and older [and ferrets 10 weeks of age and older]
- For the prevention and treatment of flea infestations
- One treatment prevents further flea infestations for up to [4 weeks] [a month]
- Kills fleas within 12 hours on cats [, 24 hours on ferrets,] and continues to prevent infestations for up to [four weeks] [a month]
- Kills fleas before they lay eggs
- Larval flea stages in the pet's environment are killed following contact with an Advantage II treated cat [or ferret]
- Kills larval stages of fleas following contact with an Advantage II treated cat [or ferret]
- Kills fleas on cats within 12 hours [and on ferrets within 24 hours] of application
- Stops existing flea infestations by killing adult fleas
- Prevents reinfestations by killing adult fleas before they lay eggs
- Reinfesting fleas on cats are killed within 2 hours with protection against further flea infestation
- [Prevents] [Stops] flea eggs from hatching [into biting adults]
- Effectively breaks the flea life cycle
- [Kills] [Controls] all flea life stages
- Comprehensive flea prevention and treatment
- 3-way flea protection ([kills] [controls]) adults, larvae, and eggs
- [Prevents] [Stops] flea eggs from developing into [(biting) (adult)] fleas
- Treatment of cats with Advantage II kills fleas and may reduce the incidence of flea allergic dermatitis [FAD] or flea bite hypersensitivity
- Flea adulticide, larvicide, and ovicide
- Kills flea eggs
- Controls flea problems
- Provides flea protection
- Controls existing fleas and flea eggs plus [and] [prevents] future flea infestations

- Advantage II may be used year-round for flea [prevention][protection]
- Contains an insect growth regulator (IGR) to kill flea eggs and prevent re-infestation
- Monthly use of Advantage II on cats kills fleas and may prevent ([flea allergy dermatitis][flea bite hypersensitivity])
- Controls existing flea infestations on your cat [or ferret] and prevents further infestations
- Prevents fleas on treated cats [or ferrets] from infesting (reinfesting)
- Remains effective after bathing
- Remains effective following shampooing
- Waterproof
- Remains effective after exposure to rain or sunlight
- Fragrance-free
- In child-resistant packaging
- Starts working through contact

Reason To Issue: To add new use on ferrets. Date: 11/07/12
Supersedes: 09/25/12

SUBSET LABELING: Cat Only Product
NOTE TO REVIEWER: [(Brackets and parentheses indicate alternate language)]

[Front Panel]

Advantage® II Small Cat

Once-A-Month Topical Flea Prevention and Treatment for Cats
For Use ONLY on Cats 8 Weeks and Older and Weighing 5 - 9 lbs.

[Selected optional claims bulleted here from page 10 and/or 11]

-
-
-
-

Active Ingredients	% By Weight
Imidacloprid	9.10%
Pyriproxyfen	0.46%
Other Ingredients	90.44%
Total	100.00%

EPA Est. No. 11556-XXX-X EPA Reg No. 11556-151

KEEP OUT OF REACH OF CHILDREN

CAUTION

See back panel for Precautionary Statements.
For Directions for Use, Storage and Disposal, and First Aid see package insert inside.

[Back Panel]

Advantage® II Small Cat

Once-A-Month Topical Flea Prevention and Treatment for Cats
For Use **ONLY** on Cats 8 Weeks and **O**lder and Weighing 5 - 9 lbs.

READ THE ENTIRE LABEL BEFORE EACH USE
For the Prevention and Treatment of Flea Infestations

PRECAUTIONARY STATEMENTS

HAZARDS TO HUMANS

CAUTION: Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling. Keep out of reach of children. Do not contaminate feed or food.

HAZARDS TO DOMESTIC ANIMALS

For external use only. Do not apply to cats or kittens under 8 weeks of age or weighing less than 5 lbs. As with any product, consult your veterinarian before using this product on debilitated, aged, pregnant or nursing cats. Individual sensitivities, while rare, may occur after using ANY pesticide product for cats. If signs persist, or become more severe, consult a veterinarian immediately. If your cat is on medication, consult your veterinarian before using this or any other product.

Side Effects: Monitor your cat after application. Side effects, although very rare, may include signs of skin irritation such as redness, scratching, or other signs of discomfort. Gastrointestinal signs such as hypersalivation, vomiting or diarrhea have also been reported. If these or other side effects (such as lethargy) occur, consult your veterinarian or call 1-800-422-9874.

For consumer questions call 1-800-255-6826.
For medical emergencies call 1-800-422-9874.

RESTRICTIONS:

- Use only on cats or kittens 8 weeks and older and weighing 5 – 9 lbs. Do not use on other animals.
- Do not apply more than one (1) tube per treatment.
- Do not have contact or allow children to have contact with treated area until completely dry.

Net Contents: [X] Tube(s), each 0.014 fl. oz. (0.4 mL)

[Sample - Not for (Re)Sale]

Manufactured For

Bayer HealthCare LLC
Animal Health Division
P.O. BOX 390
Shawnee Mission, Kansas 66201 USA

Made in Germany

[Back Panel and/or Insert]

Advantage® II Small Cat

Once-A-Month Topical Flea Prevention and Treatment for Cats
For Use ONLY on Cats 8 Weeks and Older and Weighing 5 - 9 lbs.

READ THE ENTIRE LABEL BEFORE EACH USE
For the Prevention and Treatment of Flea Infestations

DIRECTIONS FOR USE

It is a violation of Federal Law to use this product in a manner inconsistent with its labeling.

HOW TO OPEN

8. Being careful not to cut close to the blister cavities, take scissors and cut off one section of the card containing a single tube.
9. Take the separated section, and cut into the blister cavity across the small side, close to the cap of the tube.
10. Peel off the foil, and take out the tube.
11. Repeat steps 1 to 3 for each tube.

HOW TO APPLY

1. Remove one applicator tube from the package. See "HOW TO OPEN" section.

2. Hold applicator tube in an upright position facing away from you and your pet's face and eyes. Pull cap off tube.

[Visuals Depicting How to Open Applicator Tube]

3. Turn the cap around and place other end of cap back on tube.

4. Twist cap to break seal, then remove cap from tube.

12. Part the hair on the neck at the base of the skull until the skin is visible. Place the tip of the tube on the skin and squeeze the tube to expel the entire contents directly on the skin. *Do not get this product in your cat's eyes, or allow your cat to ingest this product. The product is bitter tasting and salivation may occur for a short time if the*

cat licks the product immediately after treatment. Treatment at the base of the skull will minimize the opportunity for the cat to lick the product. Do not allow the product to run off.

[Visuals Depicting Application to Animal]

13. Discard empty tube as described in Storage and Disposal.

14. Under normal conditions this product is effective for a month. However, in case of severe flea infestation, retreatment may be necessary earlier than four (4) weeks. Do not retreat more often than once every seven (7) days. After flea control is attained, return to a monthly retreatment schedule.

PRODUCT INFORMATION

The successive feeding activity of fleas on cats frequently elicits a hypersensitivity skin disorder known as flea allergy dermatitis (FAD) or flea bite hypersensitivity. Treatment of cats with Advantage® II Small Cat kills fleas and may reduce the incidence of this condition.

Advantage® II Small Cat kills the existing fleas on cats within 12 hours. Reinfesting fleas are killed within 2 hours with protection against further flea infestation lasting for up to four (4) weeks. Pre-existing pupae in the environment may continue to emerge for six (6) weeks or longer depending upon the climatic conditions.

Fleas, eggs and larvae in the cat's surroundings are killed following contact with an Advantage® II Small Cat treated cat. Advantage® II Small Cat provides multi-stage flea control effectively breaking all flea life-cycle stages for lasting control of flea populations.

Advantage® II Small Cat kills adult fleas quickly, within 12 hours, inhibits the development of immature flea life stages and prevents them from reaching the biting adult stage.

Advantage® II Small Cat is waterproof and remains effective following a shampoo treatment or after exposure to rain or sunlight.

Apply monthly treatments for optimal control and prevention of fleas.

KEEP OUT OF REACH OF CHILDREN

CAUTION

PRECAUTIONARY STATEMENTS
HAZARDS TO HUMANS

CAUTION: Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling. Keep out of reach of children. Do not contaminate feed or food.

FIRST AID	
If Swallowed:	• Call a poison control center or doctor immediately for treatment advice. • Have person sip a glass of water if able to swallow. • Do not induce vomiting unless told to do so by the poison control center or doctor. • Do not give anything to an unconscious person.
If In Eyes:	• Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 mimites, then continue rinsing eye. • Call a poison control center or doctor for treatment advice.
If On Skin	• Wash with plenty of soap and water.
HOT LINE NUMBER	
Have the product container or label with you when calling a poison control center or doctor, or going for treatment. For medical emergencies call 1-800-422-9874. For customer questions call 1-800-255-6826.	
NOTE TO PHYSICIAN	
Treat the patient symptomatically.	

HAZARDS TO DOMESTIC ANIMALS

For external use only. Do not apply to cats or kittens under 8 weeks of age or weighing less than 5 lbs. As with any product, consult your veterinarian before using this product on debilitated, aged, pregnant or nursing cats. Individual sensitivities, while rare, may occur after using ANY pesticide product for cats. If signs persist, or become more severe, consult a veterinarian immediately. If your cat is on medication, consult your veterinarian before using this or any other product.

Side Effects: Monitor your cat after application. Side effects, although very rare, may include signs of skin irritation such as redness, scratching, or other signs of discomfort. Gastrointestinal signs such as hypersalivation, vomiting or diarrhea have also been reported. If these or other side effects (such as lethargy) occur, consult your veterinarian or call 1-800-422-9874.

For medical emergencies call 1-800-422-9874.

RESTRICTIONS:

- Use only on cats or kittens 8 weeks and older and weighing 5 – 9 lbs. Do not use on other animals.
- Do not apply more than one (1) tube per treatment.
- Do not have contact or allow children to have contact with treated area until completely dry.

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal.

Pesticide Storage: Store in a cool, dry place inaccessible to children and pets. **Pesticide Disposal and Container Handling:** Nonrefillable container. **If empty:** Do not reuse or refill this container. Place in trash or offer for recycling if available. **If partly filled:** Call your local solid waste agency or 1-800-422-9874 for disposal instructions. Never place unused product down any indoor or outdoor drain.

LIMITED WARRANTY AND LIMITATION OF DAMAGES

Bayer HealthCare LLC, Animal Health Division warrants that this material conforms to the chemical description on the label. TO THE EXTENT CONSISTENT WITH APPLICABLE LAW, BAYER MAKES NO OTHER EXPRESS OR IMPLIED WARRANTY, INCLUDING ANY OTHER EXPRESS OR IMPLIED WARRANTY OF FITNESS OR MERCHANTABILITY, and no agent of Bayer is authorized to do so except in writing with a specific reference to this warranty. Any damages arising from a breach of this warranty shall be limited to direct damages and shall not include consequential commercial damages such as loss of profits or values, etc.

[Label on Individual Tube]

Advantage® II Small Cat

9.10% Imidacloprid

0.46% Pyriproxyfen

0.014 fl. oz. (0.4 mL)

EPA Reg. No. 11556-151

Keep Out of Reach of Children

CAUTION

Read The Entire Label Before Use

BAYER

Lot No. 0000000

[Label on blister card; one card containing 1, 2, 3, 4, 5, or 6 tubes]

Advantage® II Small Cat

For external use only on cats and kittens 8 weeks and older and weighing 5 - 9 lbs.

9.10% Imidacloprid

0.46% Pyriproxyfen

[X] - 0.014 fl. oz. (0.4 mL)

EPA Reg. No. 11556-151

BAYER

NOTE TO REVIEWER: [(Brackets and parentheses indicate alternate language)]

OPTIONAL MARKETING CLAIMS [Appearing on any panel]

- For use on cats and kittens 8 weeks of age and older
- Advantage II contains [imidacloprid], [and an/the] [insect growth regulator] [IGR] [pyriproxyfen]
- A single topical application remains effective for up to [4 weeks] [a month]
- Convenient, easy-to-apply topical solution
- Convenient, easy-to-apply and fragrance free [monthly] [topical solution]
- Once a month topical flea prevention and treatment for cats 8 weeks of age or older
- Advantage II is indicated for the prevention and treatment of fleas on cats 8 weeks of age and older
- For the prevention and treatment of flea infestations
- One treatment prevents further flea infestations for up to [4 weeks] [a month]
- Kills fleas on cats within [12] hours and continues to prevent infestations for up to [four weeks] [a month]
- Kills fleas before they lay eggs
- Larval flea stages in the cat's environment are killed following contact with an Advantage II treated cat
- Kills larval stages of fleas following contact with an Advantage II treated cat
- Kills fleas within [12] hours of application
- Stops existing flea infestations by killing adult fleas
- Prevents reinfestations by killing adult fleas before they lay eggs
- Reinfesting fleas are killed within 2 hours with protection against further flea infestation
- [Prevents] [Stops] flea eggs from hatching [into biting adults]
- Effectively breaks the flea life cycle
- [Kills] [Controls] all flea life stages
- Comprehensive flea prevention and treatment
- 3-way flea protection ([kills] [controls]) adults, larvae, and eggs
- [Prevents] [Stops] flea eggs from developing into [(biting) (adult)] fleas
- Treatment with Advantage II kills fleas and may reduce the incidence of flea allergic dermatitis [FAD] or flea bite hypersensitivity
- Flea adulticide, larvicide, and ovicide
- Kills flea eggs
- Controls flea problems
- Provides flea protection
- Controls existing fleas and flea eggs plus [and] [prevents] future flea infestations
- Advantage II may be used year-round for flea [prevention][protection]

- Contains an insect growth regulator (IGR) to kill flea eggs and prevent re-infestation
- Monthly use of Advantage II kills fleas and may prevent ([flea allergy dermatitis][flea bite hypersensitivity])
- Controls existing flea infestations on your cat and prevents further infestations
- Prevents fleas on treated cats from infesting (reinfesting)
- Remains effective after bathing
- Remains effective following shampooing
- Waterproof
- Remains effective after exposure to rain or sunlight
- Fragrance-free
- In child-resistant packaging
- Starts working through contact

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

OFFICE OF PESTICIDE PROGRAMS
REGISTRATION DIVISION (7505P)

October 5, 2012

Ferret Study DERs for Advantage® II Small Cat (EPA Reg. No. 11556-151)

MEMORANDUM

Subject:	Name of Pesticide Product:	Advantage® II Small Cat
	EPA Reg. No. /File Symbol:	11556-151
	DP Barcode:	404120
	Decision No:	466880
	Action Code:	R340
	PC Codes:	129099 (Imidacloprid: 9.1%)
		129032 (Pyriproxyfen: 0.46%)

From: Byron T. Backus, Ph.D., Toxicologist
Technical Review Branch
Registration Division (7505P)

Byron T. Backus
Oct-5-2012
M. Hollister
T. Leader - Tox

To: Autumn Metzger, RM 01
Insecticide-Rodenticide Branch
Registration Division (7505P)

Registrant: BAYER HEALTHCARE LLC

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt.
129099 Imidacloprid	9.10
129032 Pyriproxyfen	0.46
Other Ingredient(s):	90.44
Total:	100.00

ACTION REQUESTED: The Risk Manager requests: "Please review Bayer's companion animal study for acceptability to see if it supports the use on ferrets. Also please provide any age restriction…"

BACKGROUND: EPA Reg. No. 11556-151 is currently registered (dosage rate: 0.4 mL) for use on cats and kittens (8 weeks of age or older) weighing 5 to 9 lbs. The registrant wishes to add use (with a dosage rate of 0.4 mL) on ferrets ≥10 weeks of age and ≥1 lb. To support the ferret claim, the registrant has conducted a study (MRID 48880902) on 10-week-old ferrets. In addition, there is pilot study (MRID 48880901) in ferrets, and a proposed label (which includes use on ferrets with a minimum age of 10 weeks, a minimum weight of 1 lb, a dosage rate of 0.4 mL/ferret/application, and a statement to not retreat more often than every 14 days).

COMMENTS AND RECOMMENDATIONS:

1. The following is the executive summary for the ferret study in MRID 48880902:

   In a 28-day companion animal safety study (MRID 48880902), M880 Insecticide [9.1% (w/v) Imidacloprid and 0.46% (w/v) Pyriproxyfen; Lot No. KP055JX] was applied topically to two groups of six male and six female 10-week-old ferrets at 3X (1.2 mL) or 5X (2.0 mL) total dosing volumes (nominally 119.7 or 199.5 mg Imidacloprid per animal and 6.0 or 10.1 mg Pyriproxyfen per animal). The mean weight of the 5X males on Day -1 was 0.581 kg (=1.28 lbs) and for the 5X females it was 0.467 kg (=1.03 lbs). M880 Insecticide Placebo (Lot No. 08-05-30) was applied in identical manner to a vehicle control group of 6 male and 6 female animals at a total dosing volume of 1.8 mL (inert ingredients at the maximum levels that would appear in the 5X formulation). The test article or vehicle control was applied topically, using a calibrated pipette, directly to the skin on the dorsal midline from the base of the skull to the interscapular region. To achieve the 3X and 5X doses, the appropriate volume of the test material was applied on either three or five occasions with approximately one hour between the applications; vehicle controls were given five equally sized applications, at approximately one-hour intervals. The animals were treated twice, at a 14-day interval (on days 0 and 14) and remained on study for 14 days after the final treatment. A pilot study (MRID 48880901) was conducted to determine the appropriate minimum age of the animals and to preliminarily evaluate safety.

   On day 1, one vehicle control female exhibited ataxia, abnormal locomotion, biting at the cage flooring, seizure activity, and hypothermia (body temperature of 95.0° F). This animal was euthanized on day 2 due to inability to control the seizure activity with supportive care and medication. Transient local effects were seen at all the application sites, including matted, wet, and/or greasy appearance. Treatment of 10-week-old ferrets with the test material at 3X or 5X the proposed use rate did not result in relevant differences in body weight, food consumption, or evaluated hematological and chemistry parameters. However, in the reviewer's opinion, application of the excipients at the maximum levels that would appear in a 5X dosage of the end-use product (but without active ingredients present) *may* have resulted in toxicity, which was evident as weight losses following the second application (on day 14) and possibly as the uncontrolled seizure activity of the vehicle control animal on day 1.

   It is concluded that the margin of safety in 10-week-old ferrets exposed topically to M880 Insecticide (Advantage® II Small Cat) twice, at 14-day intervals, is at least 5X the recommended dose of 0.4 mL per *animal*. The margin of safety of the inert ingredients, together in the concentrations that would be present in the end-use product (but without active ingredients present), has *not* been established. As the mean weight of the 5X males on Day -1 was 0.581 kg (=1.28 lbs) and for the 5X females was 0.467 kg (=1.03 lbs), the Agency can accept the claim for use on ferrets ≥10 weeks of age and weighing 1 lb or more.

This companion animal safety study in pediatric ferrets is **Acceptable** and **does satisfy** the guideline requirement for a companion animal safety study (OCSPP 870.7200) in pediatric ferrets.

2. Although this study was conducted in young or "pediatric" ferrets, TRB concludes that the study also supports use in adult ferrets, as a precedent has been set in a previously registered product (EPA Reg. No. 67505-5). The supporting study (MRID 44756102) for 67505-5 utilized 16-19 week-old ferrets. The only age restriction imposed on EPA Reg. No. 67505-5 was that ferrets had to be 16 weeks or older.

3. The study in MRID 48880902 adequately supports the proposed label claims and uses for EPA Reg. No. 11556-151 with respect to ferrets (including a minimum age of 10 weeks, a minimum weight of 1 lb, a dosage rate of 0.4 mL/ferret/application, and a statement to not retreat more often than every 14 days).

4. The following is from the executive summary for MRID 48880901:

   A two-phase pilot companion animal safety study (MRID 48880901) preliminarily evaluated the safety of M880 Insecticide [9.1% (w/v) Imidacloprid and 0.46% (w/v) Pyriproxyfen; Lot No. KP06T8L KP06 SOR] in pediatric ferrets. In Phase 1, the test material was applied topically to groups of three male and three female ferrets that were 8-, 12-, or 16-weeks-old (±2 days) at total dosing volumes of 2.0 mL/animal, i.e., 5X the intended label-recommended dosing volume. Mineral oil or M880 Insecticide Placebo (the final formulation minus the active ingredients) were applied to two additional (control) groups of two male and two female 8-week-old ferrets at total dosing volumes of either 2.0 mL/animal (mineral oil) or 1.8 mL/animal (M880 Insecticide Placebo, to give inert ingredients at the maximum levels that would appear in the 5X formulation). In Phase 2, a group of five male and three female 10-week-old (±1 day) ferrets were treated with M880 Insecticide Placebo at a total volume of 1.8 mL/animal, i.e., 5X the intended label-recommended dosing volume of the inert ingredients. In both phases, the test material or vehicle was applied to the interscapular region of each animal via calibrated pipette or via the polypropylene tube in which the test material was packaged, with the total dosing volume achieved through five equally sized "sub-applications" that were either 0.4 mL or 0.36 mL apiece, as appropriate, and given at 60-minute intervals. Treatment was on day 0, and the animals were observed for up to four days with the routinely evaluated parameters including body weight, food consumption, and hematology/clinical chemistry. The second phase was added to the study due to deaths of two 8-week-old 5X vehicle control ferrets during Phase 1.

   During the post-treatment observations on day 0, all study animals were observed to have matted, greasy, and/or spiked hair at the dose site, i.e., from the base of the head to the interscapular region

   Based on the results of this study, 10-week-old ferrets were used in the definitive companion animal safety study.

DATA EVALUATION RECORD

PYRIPROXYFEN AND IMIDACLOPRID
[M880 INSECTICIDE; ADVANTAGE® II SMALL CAT]

STUDY TYPE: COMPANION ANIMAL SAFETY STUDY- PEDIATRIC FERRETS; NON-GUIDELINE

MRIDS 488809-02 and 488809-01

Prepared for

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Task Order No. 3-C-11

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Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

EPA Reviewer: Byron T. Backus, Ph.D. **Signature:** Byron T. Backus
Technical Review Branch, Registration Division (7505P) **Date:** Oct. 5, 2012

Template version 02/06

DATA EVALUATION RECORD

STUDY TYPE: Companion Animal Safety Study - Pediatric ferrets; Non-guideline

PC CODES: 129032, 129099 **DP BARCODE:** 404120

TEST MATERIAL (PURITY): M880 Insecticide [9.1% (w/v) Imidacloprid and 0.46% (w/v) Pyriproxyfen; Lot No. KP055JX]

SYNONYMS: Advantage® II Small Cat

CITATIONS: Madsen, T. (2012) Evaluation of the general safety of M880 on 10-week-old ferrets. Sinclair Research Center, LLC (SRC), Auxvasse, Missouri. Study Number S10960, April 25, 2012. MRID 48880902. Unpublished.

Madsen, T. (2012) Pilot general safety evaluation of M880 Insecticide on pediatric ferrets. Sinclair Research Center, LLC (SRC), Auxvasse, Missouri. Study Number S10986A, April 25, 2012. MRID 48880901. Unpublished.

SPONSOR: Bayer HealthCare LLC / Animal Health Division, 12809 Shawnee Mission Parkway, Shawnee Mission, Kansas.

EXECUTIVE SUMMARY: In a 28-day companion animal safety study (MRID 48880902), M880 Insecticide [9.1% (w/v) Imidacloprid and 0.46% (w/v) Pyriproxyfen; Lot No. KP055JX] was applied topically to two groups of six male and six female 10-week-old ferrets at 3X (1.2 mL) or 5X (2.0 mL) total dosing volumes (nominally 119.7 or 199.5 mg Imidacloprid per animal and 6.0 or 10.1 mg Pyriproxyfen per animal). The mean weight of the 5X males on Day -1 was 0.581 kg (=1.28 lbs) and for the 5X females it was 0.467 kg (=1.03 lbs). M880 Insecticide Placebo (Lot No. 08-05-30) was applied in identical manner to a vehicle control group of 6 male and 6 female animals at a total dosing volume of 1.8 mL (inert ingredients at the maximum levels that would appear in the 5X formulation). The test article or vehicle control was applied topically, using a calibrated pipette, directly to the skin on the dorsal midline from the base of the skull to the interscapular region. To achieve the 3X and 5X doses, the appropriate volume of the test material was applied on either three or five occasions with approximately one hour between the applications; vehicle controls were given five equally sized applications, at approximately one-hour intervals. The animals were treated twice, at a 14-day interval (on days 0 and 14) and remained on study for 14 days after the final treatment. A pilot study (MRID 48880901) was conducted to determine the appropriate minimum age of the animals and to preliminarily evaluate safety.

On day 1, one vehicle control female exhibited ataxia, abnormal locomotion, biting at the cage flooring, seizure activity, and hypothermia (body temperature of 95.0° F). This animal was euthanized on day 2 due to inability to control the seizure activity with supportive care and medication. Transient local effects were seen at all the application sites, including matted, wet, and/or greasy appearance. Treatment of 10-week-old ferrets with the test material at 3X or 5X the proposed

use rate did not result in relevant differences in body weight, food consumption, or evaluated hematological and chemistry parameters. However, in the reviewer's opinion, application of the excipients at the maximum levels that would appear in a 5X dosage of the end-use product (but without active ingredients present) *may* have resulted in toxicity, which was evident as weight losses following the second application (on day 14) and possibly as the uncontrolled seizure activity of the vehicle control animal on day 1.

It is concluded that the margin of safety in 10-week-old ferrets exposed topically to M880 Insecticide (Advantage® II Small Cat) twice, at 14-day intervals, is at least 5X the recommended dose of 0.4 mL per *animal*. The margin of safety of the inert ingredients, together in the concentrations that would be present in the end-use product (but without active ingredients present), has *not* been established. As the mean weight of the 5X males on Day -1 was 0.581 kg (=1.28 lbs) and for the 5X females was 0.467 kg (=1.03 lbs), the Agency can accept the claim for use on ferrets ≥10 weeks of age and weighing 1 lb or more.

This companion animal safety study in pediatric ferrets is **Acceptable** and **does satisfy** the guideline requirement for a companion animal safety study (OCSPP 870.7200) in pediatric ferrets.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided in MRID 48880902. Signed and dated GLP and Data Confidentiality statements were provided in MRID 48880901; according to the GLP statement, the pilot study was *not* conducted in compliance with the GLP regulations set forth in 40 CFR Part 160.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: M880 Insecticide (Advantage® II Small Cat; EPA Reg. No. 11556-151)

Description:	Clear amber liquid
Lot #:	KP055JX, according to p. 13; however, the certificate of analysis on p. 82 gave the Lot # as KP005JX
Purity:	9.1% w/v Imidacloprid and 0.46% w/v Pyriproxyfen (nominally); measured at 8.8-9.0% Imidacloprid and 0.45-0.48% Pyriproxyfen.
Compound Stability:	Confirmed analytically; stored at room temperature in amber glass bottles.
CAS #:	Imidacloprid: 138261-41-3; pyriproxyfen: 95737-68-1

2. Vehicle and/or positive control: The final formulation minus the active ingredients (M880 Insecticide Placebo, Lot No. 08-05-30) was used as a vehicle control; this was a clear amber liquid, stored in amber glass bottles at room temperature. No positive control was used.

3. Test animals: Ferrets

Species:	*Mustela putorius furo*
Breed:	N/a
Age/weight at study initiation:	69-71 days old / Males: 431-730 g; Females: 354-541 g.
Source:	Marshall BioResources (North Rose, N.Y.)
Housing:	Individually in stainless steel cages with a mesh front gate and mesh flooring (1.9 square feet of floor space per animal)
Diet:	Marshall Premium Ferret Diet dry food (Marshall Diets, Wolcott, N.Y.), *ad libitum*; ferrets exhibiting inappetence, i.e., consuming <25 grams of dry food per day, were offered moist food along with their daily dry ration.
Water:	*Ad libitum* tap water, sourced from an on-site deep well
Environmental conditions:	**Temperature:** 55.9-74.8° F. **Humidity:** 15-98% **Air changes:** "appropriate hourly air exchanges" **Photoperiod:** 12 hrs light/12 hrs dark
Acclimation period:	Seven or eight days

B. STUDY DESIGN:

1. In life dates: Start: October 18, 2011 (Day 0, Replicate 1); End: November 29, 2011 (Day 28, Replicate 2).

2. Animal assignment: Study design is given in Table 1. Animals were selected for inclusion in the study according to the results of pretreatment clinical examinations, hematology, and clinical chemistry; exclusion criteria included failure to maintain or gain body weight (during acclimation), congenital defects, need for concomitant medical therapy, and intractability or fractiousness. Due to poor health among the initial shipment of animals, e.g. failure to thrive (maintain or gain body weight) for a "substantial number" of animals and two deaths and four euthanasias due to critical decline in condition during acclimation, the study design was altered to use two equal replicates of 18 animals each (9 males and 9 females, 3/sex/group). According to the study protocol (Appendix 1, p. 36), the animals were assigned to groups on day -1, using a

randomized block design, in which animals were blocked by sex, ranked in descending body weight order, and assigned to the treatment groups using pre-generated random numbers, with final adjustments made if needed to equally distribute littermates across all treatment groups as much as possible.

TABLE 1: Study design [a]			
Test Group	Dosing volume (mL/animal)	Number assigned	
		Males	Females
1. 3X	1.2 mL (3 applications of 0.4 mL of test item)	6	6
2. 5X	2.0 mL (5 applications of 0.4 mL of test item)	6	6
3. Vehicle Control	1.8 mL (5 applications of 0.36 mL of control item)	6	6

[a] Data taken from p. 12, MRID 48880902.

3. **Dose selection rationale:** The dose levels and dosing schedule were based on OCSPP 870.7200 and discussions between Bayer and EPA during a pre-study conference in Washington D.C. on March 1, 2011. The intended therapeutic dose is 0.4 mL/ferret, and according to the provided sample labeling, the proposed retreatment interval for ferrets is ≥14 days.

4. **Treatment:** On days 0 and 14, the control or test material, as appropriate, was applied topically, using a calibrated pipette, directly to the skin on the dorsal midline from the base of the skull to the interscapular region. To achieve the exaggerated 3X and 5X doses, the appropriate volume of the appropriate material was applied on either three or five occasions with approximately one hour between the applications.

5. **Concomitant treatments:** Due to positive fecal results for giardia in several Replicate 1 animals during acclimation, the animals were treated with metronidazole (35 mg/kg, once per day, for up to 5 days) as follows: all Replicate 1 animals were treated on days 3-7 and 21-25; and all Replicate 2 animals were treated on days -7 to -4, 3-7, and 19-23. The decision to treat was made based on discussion with EPA on October 17, 2011, with the agreement that the metronidazole would not be given within three days of treatment with the test or control substances in order to avoid potential confounding of the study results.

6. **Statistics:** Data from the groups treated with 3X and 5X multiples of the recommended dose were compared to data from the vehicle control group.

   The individual animal was the experimental unit. Body weight and the hematology and clinical pathology parameters (except for GGT and Heinz bodies) were analyzed using a repeated measures analysis of covariance (RMANCOVA) with treatment and sex as fixed effects in the model, replicate as a random effect, and the pretreatment baseline as a covariate. The two-way interactions "treatment by time," "treatment by sex," "sex by time," and the three-way interaction "treatment by time by sex."

   For variables measured at equally spaced intervals, four covariance structures were compared using the Akaike Information Criterion (AIC). These were compound symmetry, heterogeneous compound symmetry, first order autoregressive, and heterogeneous first order autoregressive. For variables measured at unequally spaced intervals, three covariance structures were compared:

compound symmetry, heterogeneous compound symmetry, and spatial power. Representative parameters were evaluated (i.e., glucose for clinical chemistry or hemoglobin for hematology), and the model with the lowest AIC value was applied to the remaining parameters in that category.

If the "treatment by time by sex" interaction was significant ($p \leq 0.05$), the statistical analysis of the variable was deemed inconclusive, and no further statistical analysis was conducted. If the "treatment by sex" interaction, "treatment by time" interaction, or overall treatment effect was significant ($p \leq 0.05$), pair-wise comparisons were made between+n negative controls vs. 3X and 5X. If the "treatment by sex" interaction was significant, the two sexes were evaluated separately; otherwise, comparisons were made using the combined sexes.

GGT and Heinz bodies were evaluated using Fisher's exact test

The food consumption data were not analyzed statistically.

In the opinion of the reviewer, the data should have been analyzed separately by sex, regardless of whether the "treatment by sex" interaction was significant.

C. METHODS:

1. Observations:

a. General health observations: During acclimation and the treatment interval, the animals were observed twice per day, morning and afternoon. On days 0 and 14 (treatment days), the animals were also observed pre-treatment and 1, 2, 3, and 4 hours (± 15 minutes) following the final application, and on days 1 and 15 additional observations were made at 8:00 a.m., 11:00 a.m., and 3:00 p.m. (all ±15 minutes).

b. Clinical assessments: The animals received physical examinations on day -7 or day -6 (for replicates 1 and 2, respectively) and days -4, 1, 15, and 28. Observations made during the physical examinations were not reported.

2. Body weight: The animals were weighed on days -7, -3, -1, 6, 13, 20, and 28.

3. Food consumption: Food consumption was measured daily, at approximately the same time each day (± one hour). Exact measurement was not possible because food spilled into the cage tray often became adulterated with animal waste and/or spilled water.

4. Hematology and clinical chemistry: Pre-treatment (on day -7 or day -6 for replicates 1 and 2, respectively) and on days 1, 15, and 28, blood was collected for hematology, clinical chemistry, and coagulation evaluation. Venipuncture site(s) and sampling order were not reported. The animals were anesthetized with 0.5-5% isoflurane in 100% oxygen prior to sample collection; there was no mention of prior fasting. The CHECKED (X) parameters were examined.

a. **Hematology:**

X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc.(MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)*
X	Platelet count		Reticulocyte count
	Blood clotting measurements		Morphology (blood smear)
	(Thromboplastin time)*	X	Heinz bodies
	(Clotting time)		
	(Prothrombin time)*		

* Recommended for companion animals safety evaluation based on OCSPP 870.7200.

b. **Clinical Chemistry:**

	ELECTROLYTES		OTHER
X	Calcium*	X	Albumin*
X	Chloride*	X	Creatinine*
	Magnesium	X	Urea nitrogen (BUN)*
X	Phosphorus*		Cholesterol
X	Potassium*	X	Globulins*
X	Sodium*	X	Glucose*
	ENZYMES	X	Total bilirubin*
X	Alkaline phosphatase (ALK)*	X	Direct bilirubin*
	Cholinesterase (ChE)		Indirect bilirubin
X	Creatine phosphokinase	X	Total protein (TP)*
	Lactic acid dehydrogenase (LDH)		Triglycerides
X	Alanine aminotransferase (ALT/also SGPT)*		Serum protein electrophoresis
X	Aspartate aminotransferase (AST/also SGOT)*		Albumin/globulin ratio
	Sorbitol dehydrogenase		Bicarbonate
X	Gamma glutamyl transferase (GGT)		
	Glutamate dehydrogenase		
	Amylase		

* Recommended for a companion animal safety evaluation based on OCSPP 870.7200.

[a] Only determined if total bilirubin was greater than 20 µmol/L.

5. **Urinalysis:** Urinalysis is not required for companion animal safety studies and was not done as part of the current study.

6. **Fecal analysis:** Fecal examinations were done on days -7 and 2. The results were not reported.

7. **Sacrifice and pathology:** Terminal sacrifices and gross necropsies were not done and are not required under OCSPP 870.7200. Two animals that died during acclimation, and one study animal that was euthanized for humane purposes on day 2 were subjected to necropsy. The study author stated that a post-mortem examination and diagnostic procedures appropriate for determination of the cause of illness or death (e.g., bacteriology, virology, gross pathology, histopathology, and toxicology) were arranged for each animal; however, the necropsy procedure and specific tissues that were collected were not described in the study report, and the specific

tests that were done and their results were not provided, except as a brief and not necessarily all-inclusive summary in the text.

II. RESULTS

A. **EXPOSURE:** The doses administered to the animals on a mg/kg body weight basis are given in Table 2. Because the animals gained weight between day -1 and day 13, the dosages decreased.

TABLE 2: Dosages of the active ingredients on a mg/kg body weight basis [a]

Test Group	Dosing volume (mL/animal)	Dose (mg/animal)		Day 0 Dose (mg/kg) [b]		Day 14 Dose (mg/kg) [c]	
		Imidacloprid	Pyriproxyfen	Imidacloprid	Pyriproxyfen	Imidacloprid	Pyriproxyfen
1. 3X	1.2 mL	119.7	6.0	164.0-281.0	8.2-14.1	148.9-261.4	7.5-13.1
2. 5X	2.0 mL	199.5	10.1	299.1-563.6	15.1-28.5	261.5-415.6	13.2-21.0

[a] Calculated by reviewer, using a product density of 1.096 g/mL (Bayer HealthCare Safety Data Sheet, 06/08/2011).

[b] Day -1 body weight ranges were 0.426-0.730 kg and 0.354-0.667 kg for the 3X and 5X groups, respectively.

[c] Day 13 body weight ranges were 0.458-0.804 kg and 0.480-0.763 kg for the 3X and 5X groups, respectively.

B. **OBSERVATIONS:**

1. **Mortality and clinical signs:** On day 1, one vehicle control female exhibited ataxia, abnormal locomotion, biting at the cage flooring, seizure activity, and hypothermia (body temperature of 95.0° F). This animal was euthanized on day 2 due to inability to control the seizure activity with supportive care and medication.

   All of the other animals exhibited soft and/or mucoid feces on multiple occasions, i.e., on three to nineteen days, during the study. The incidences appeared similar among groups, and there were no clear temporal relationships to treatments with the test and control articles or to treatments with the metronidazole. The soft and/or mucoid feces were therefore considered unrelated to treatment. Less common abnormal clinical signs included vomiting from one vehicle control female (day 1) and two 3X males (one each on days 5 and 17), diarrhea from one 3X male on days 23-24, sporadic unilateral ocular discharge from one 3X male and one 5X female, and "penial issues" in one 3X male on days 19 and 23; none of these were considered treatment-related.

   The study author stated that the physical examination findings for all animals were within normal limits during the scheduled physical examinations conducted during the study.

2. **Local effects at the application sites:** The study author stated that all of the animals had transient changes to the hair coat at the dose site, including matted, wet, and/or greasy appearance (p. 24). These observations were not included in the tabulated abnormal clinical observations.

C. **BODY WEIGHT AND WEIGHT GAIN:** Selected body weight data are given in Table 3. There were no clear treatment-related effects on body weight or body weight gain of the animals treated at 3X and 5X. All of the individual animals gained weight between successive measurements during acclimation and through either day 6 (for Replicate 2) or day 13 (for Replicate 1), and all of the animals had net body weight gain during days -1 to 28. Three, five,

and two animals from the Replicate 1 vehicle control, 3X, and 5X groups (respectively) lost weight between days 6 and 13, but a similar effect was not seen in Replicate 2. The vehicle control males and females had decreased body weight gain during days 13-20, which was due to large weight losses (of 103-108 g) by one male and one female; in fact five (of eleven) vehicle controls lost weight during that study interval (four Replicate 1 animals and 1 Replicate 2 animal).

TABLE 3: Body weight data (kg) [a]

Parameter/ Study day or interval		Dosage		
		3X	5X	Vehicle Controls
Males				
Body Weight:	Day -1	0.594±0.777	0.581±0.063	0.604±0.101
	Day 6	0.654±0.070	0.679±0.075	0.691±0.111
	Day 13	0.693±0.105	0.695±0.081	0.708±0.117
	Day 20	0.717±0.087	0.739±0.111	0.714±0.123
	Day 28	0.769±0.161	0.782±0.139	0.742±0.128
BW gain [b]:	Days -1 to 6	0.060	0.098	0.087
	Days 6 to 13	0.039	0.016	0.017
	Days 13 to 20	0.024	0.044	0.006
	Days 20 to 28	0.052	0.043	0.028
	Days -1 to 28	0.175	0.201	0.138
Females				
Body Weight:	Day -1	0.472±0.037	0.467±0.062	0.468±0.028
	Day 6	0.489±0.055	0.513±0.068	0.545±0.027
	Day 13	0.503±0.043	0.564±0.058	0.564±0.051
	Day 20	0.577±0.056	0.593±0.035	0.565±0.061
	Day 28	0.598±0.061	0.636±0.057	0.591±0.028
BW gain [b]:	Days -1 to 6	0.017	0.046	0.077
	Days 6 to 13	0.014	0.051	0.019
	Days 13 to 20	0.074	0.029	0.001
	Days 20 to 28	0.021	0.043	0.026
	Days -1 to 28	0.126	0.169	0.123

[a] Data taken from p. 90, MRID 48880902. Values are Mean ± Standard Deviation (where available), with n=6 for all groups initially, and n=5 for female vehicle controls after day 1.

[b] Calculated by reviewer using group mean body weight values; not analyzed statistically.

D. FOOD CONSUMPTION: The individual and group mean food consumption values fluctuated sporadically from one week to the next, without any clear relationship to treatment. In some cases the decreases corresponded to weight loss by individual animals, but in many cases they did not.

E. BLOOD ANALYSES:

1. **Hematology:** There were no treatment-related changes in any of the evaluated parameters. There were statistically significant decreases in the day 28 absolute eosinophil count and the day 28 percentage eosinophils of the 5X group relative to the vehicle control group. The differences were small in magnitude and considered biologically insignificant in the absence of correlated changes

in other leukogram parameters. There was also a statistically significant decrease in MCH of the 3X group, overall, as compared to the vehicle control group; however, examination of the mean values of the individual sexes at the separate time points did not reveal any biologically significant differences between groups, and there were no correlated changes in other erythrocyte parameters indicative of anemia.

It should be noted that several Replicate 1 animals exhibited neutrophilic leukocytosis with lymphopenia during acclimation, consistent with inflammation or illness.

2. **Clinical Chemistry:** There were statistically significant decreases in the sodium and chloride levels of the 3X and 5X groups overall, as compared with the vehicle control group. However, when the data for the individual sexes at each separate time point were examined, the differences from vehicle control lacked a dose response, the mean values fell within two standard deviations of the vehicle control mean, and the magnitude of the differences was quite small.

   Clinical chemistry findings from the day 1 blood sample from the animal that was euthanized on day 2 included low serum calcium (4.9 mg/dL vs. reference range of 7.7-11.0 mg/dL), slightly increased blood glucose (147 mg/dL vs. normal range of 62.5-134 mg/dL), increased urea nitrogen (67 mg/dL vs. 10-33 mg/dL), increased sodium and chloride levels, decreased potassium (3.8 mmol/L vs. 4.3-5.8 mmol/L), increased creatine phosphokinase activity (5106 U/L), and mild increases in alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase activities (in the face of normal gamma glutamyl transpeptidase activity). These changes are consistent with recent prior (undetected) seizure activity in this animal. Approximately five minutes after intraperitoneal administration of 0.5 mL of 50% dextrose as treatment for suspected hypoglycemia, blood glucose was determined to be 287 mg/dL. [Note: administration of dextrose may have resulted in a false impression of hyperglycemia.]

F. **SACRIFICE AND PATHOLOGY:** The study author stated (p. 28) that necropsy and histopathology findings from the animal euthanized on day 2 included acute neuronal necrosis due to hypoxia of seizure and the presence of *Helicobacter mustelae* in the gastric mucosa. A full pathology/histopathology report was not provided.

III. DISCUSSION and CONCLUSIONS

A. **INVESTIGATORS' CONCLUSIONS:** M880 administration to 10-week-old ferrets at 3X or 5X the proposed use rate only resulted in transient changes of the hair coat and abnormal feces, and similar findings were also noted for 10-week-old ferrets treated with 5X vehicle control. There were no treatment-related or biologically relevant differences in body weight, food consumption, or the evaluated hematological and chemistry parameters, and no abnormal trends or clinically relevant differences were observed between scheduled pre- and post-dose clinical pathology for animals in the vehicle control or test substance groups.

One animal in the 5X vehicle control group (3F5:788) was humanely euthanized on study day 2 of Replicate 2 (November 3, 2011) due to uncontrolled seizure activity, and a full necropsy with histopathologic evaluation of tissues was performed. Histopathologic findings included acute neuronal necrosis in the cerebral cortex and microscopic identification of *Helicobacter mustelae*. The observed seizure activity was attributed to idiopathic epilepsy exacerbated by *H. mustelae* infection. This conclusion was based on the following.

- Seizure activity was noted on November 5, 2011 for another ferret from the same shipment, which had remained in the testing facility's open colony after randomization procedures. Diagnostic findings from this animal included neuronal degeneration/necrosis similar to that seen for 3F5:788, but no evidence of *H. mustelae* was recorded. Canine distemper virus was isolated via PCR although the animal had been previously vaccinated, and no other clinical signs of distemper, such as the nasal and ocular discharge and dermatitis around the chin and lips that typically occur prior to signs of neurotropic disease, were observed prior to the seizure event.

- During the acclimation period for Replicate 1, fluctuations in, or absence of, anticipated body weight gain were noted for a large number of individuals in the potential study pool and for animals of similar age obtained from the same supplier during the same period for potential use in an unrelated study. Eight (of sixty) ferrets were humanely euthanized due to failure to thrive and disqualification from potential study inclusion, but, in accordance with standard culling procedure of the testing laboratory, these animals were not necropsied. Six additional animals died acutely or were euthanized due to critical decline in condition, and gross findings in these animals included hemorrhagic gastrointestinal disease characterized by the presence of dark, red material in the stomach or intestinal tract. Initial differential diagnoses for several of the animals that died acutely without precipitating health issues included giardiasis, coccidiosis, and toxemia of clostridial disease.

- Communications with the animal supplier confirmed that occasional increases in juvenile ferret mortality are seen in the supplier's colony. Clinical signs prior to death described by the supplier included ill thrift or failure to thrive, similar to observations recorded among affected animals in the pilot and pivotal study pools.

- An ongoing literature review and further evaluation of available tissues from affected animals implicated the bacterium *H. mustelae* as the most likely cause of the observed fatalities and failure to thrive during the acclimation period and, potentially, the intermittent weight loss observed during the in-life period. *H. mustelae* was identified in the tissues of four of the six animals found dead or euthanized for acute deterioration. *H. mustelae* infection can result in severe deterioration and/or acute death in ferrets.[i] It is difficult to detect microscopically and is a common commensal in many ferret colonies. According to R.S. Ball, a consultant with Marshall BioResources, "Conventionally reared ferrets are presumptively *H. mustelae* positive, with disease becoming manifest as the result of stresses such as weaning, other illness, or experimental manipulations."[i]

- According to the study author, review of the literature further pointed to *H. mustelae* as the underlying cause for Animal 3F5:788's condition. Due to similar pathogenesis, ferrets have been used as research models to investigate the impact and treatment of *H. pylori* in humans.[ii, iii] The role of *H. pylori* has been suggested for a number of extra-intestinal disease processes in humans, including idiopathic epilepsy.[iv] Regarding *H. pylori* and idiopathic epilepsy in humans, the study author mentioned that hypotheses include an immunological mechanism involving antibodies against the agent and that research has demonstrated higher seroprevalence of *H. pylori* for patients with idiopathic epilepsy as well as a significant difference in prognosis for infected versus non-infected patients.[v, vi] In other work, eradication of *H. pylori* resulted in resolution of clinical symptoms.[vii]

B. REVIEWER COMMENTS:

The reviewer agrees that treatment of 10-week-old ferrets with the test material at 3X or 5X the proposed use rate resulted in transient changes of the hair coat and did not result in relevant differences in body weight, food consumption, or the evaluated hematological and chemistry parameters. However, in the reviewer's opinion, application of the excipients at the maximum levels that would appear in a 5X dosage of the end-use product (but without active ingredients present) *may* have resulted in toxicity, which was evident as weight losses following the second application (on day 14) and possibly as the uncontrolled seizure activity of one animal on day 1.

The reviewer disagrees with the study author's conclusion that the observed seizure activity of one vehicle control female can be attributed to idiopathic epilepsy exacerbated by *H. mustelae* infection. Certainly *H. mustelae* infection can exacerbate the effects of "stress," other health problems, or even toxicity; however, it is extremely unlikely that this animal had idiopathic epilepsy, which, according to at least one subject-matter expert, "has not been reported in ferrets."[viii] It is the opinion of the reviewer that involvement of the vehicle control cannot be definitively ruled out based on the available data.

Insufficient information was provided to fully evaluate the significance of the later seizure activity of another ferret from the same shipment, which was not assigned to the current study. The study author stated that no evidence of *H. mustelae* was recorded, that canine distemper virus was isolated via PCR, that the animal had been previously vaccinated, and that no other clinical signs of distemper were observed prior to the seizure event. The study author did *not* report which specific vaccine was given, when the vaccine was given, or whether the unassigned ferret was left un-boostered after arrival at the testing facility, like the animals that were assigned to the current study. It is also unknown whether any samples from the vehicle control female (#3F5:788) were submitted for distemper testing and/or testing for other viruses, and, if so, what the results were. Under the given circumstances, it is possible that the PCR result from the unassigned animal was a false positive, due to prior vaccination, or that the animal contracted canine distemper either because it was not fully vaccinated or due to vaccine failure. It is also possible that one or both animals had post-vaccinal encephalitis.

The study author mentioned that occasional increases in juvenile ferret mortality are seen in the supplier's colony and that the clinical signs prior to death in these cases are similar to observations recorded among affected animals in the pilot and definitive study pools, namely "ill thrift" or "failure to thrive." However, "ill thrift" and "failure to thrive" are nonspecific and could be due to any number of things instead of or in addition to *H. mustelae.* In fact, some possible explanations for these observations were found to be present in ferrets at the testing facility, including giardia, corona viridae or parvo virus, both of which were found in two animals that died during the acclimation period for Replicate 1, and Isospora, which was found in one animal in the shipment intended for Replicate 2.

Together with the body weight effect seen in this study, the fact that problems potentially attributable to the *H. mustelae* organism were only seen in vehicle control animals in both the current study and the pilot study is suggestive of vehicle-related toxicity. It is possible that one of the inert ingredients or the combination thereof is problematic for ferrets, and, if so, the question is whether the ingredient(s) could pose a problem under use conditions. However, it is noted that

this study attained the 3X and 5X exaggerated doses through modified use of the actual end-use product, rather than using specifically prepared formulations that contained higher concentrations of the active ingredient. This means that the animals in the 5X-treated group were exposed to 5X levels of all the excipients without exhibiting the same degree of toxicity seen in the animals of the vehicle control group. It is unknown why this would happen, but this phenomenon has been observed previously, in studies with other end-use products. Two possible explanations are 1) that a difference in viscosity of the vehicle compared to the end-use product may have resulted in greater skin penetration of the former, or 2) that the absence of the active ingredients made the formulation less unpalatable, so that the animals were grooming themselves more readily, thus ingesting a greater quantity of the excipients.

It is concluded that the margin of safety in 10-week-old ferrets exposed topically to M880 Insecticide (Advantage® II Small Cat) twice, at 14-day intervals, is at least 5X the recommended dose of 0.4 mL per *animal.* The margin of safety of the inert ingredients, together in the concentrations that would be present in the end-use product (but without active ingredients present), has *not* been established. As the mean weight of the 5X males on Day -1 was 0.581 kg (=1.28 lbs) and for the 5X females was 0.467 kg (=1.03 lbs), the study in MRID 48880902 supports the use of EPA Reg. No. 11556-151 at a dosage rate of 0.4 mL on ferrets ≥10 weeks of age and weighing 1 lb or more, with applications at no less than two week intervals.

C. **STUDY DEFICIENCIES:** The study deviated from OCSPP 870.7200 with respect to the following:

- Prothrombin time and activated partial thromboplastin time were not evaluated. Presumably these tests were omitted due to the small size of the samples attainable from the animals used. The Agency has an adult cat companion animal safety study (MRID 45097001) from the registrant that was conducted on a formulation containing 9.1% imidacloprid and 0.9% pyriproxyfen in which there was no effect on prothrombin time. In addition, the Agency has an adult dog companion animal safety study (MRID 45097102) and a puppy companion animal safety study (MRID 45097101) conducted on a formulation containing 9.1% imidacloporid and 0.9% pyriproxyfen in which there were no effects on prothrombin time or activated partial thromboplastin time. Based on phylogenetic considerations, it is extremely unlikely that ferrets would show an effect involving these parameters.
- The method of administration used in the study was not identical to that of the end-use product.
- A full pathology/histopathology report was not provided for the vehicle control animal that was sacrificed due to inability to bring seizures under control.
- According to OCSPP 870.7200, animals should be vaccinated, dewormed, and acclimated for 2 weeks prior to the initiation of the study. The longer acclimation period would have allowed for *both* replicates to be treated for giardia prior to the initial treatment.

IV. REFERENCES:

[i] R.S. Ball. Issues to Consider for Preparing Ferrets as Research Subjects in the Laboratory. ILAR J. 2006;47(4), p. 353.

[ii] J.G. Fox, P. Correa, et al. Helicobacter mustelae-associated gastritis in ferrets. An animal model of Helicobacter pylori gastritis in humans. Gastroenterology. 1990 Aug;99(2), pp. 352-61.

[iii] J.G. Fox in Biology and Diseases of the Ferret, 2nd edn (ed. Fox, J.G.). Lippincott Williams and Wilkins, Baltimore. 1998, Ch. 14.

[iv] M.U. Farooq, A. Bhett. Helicobacter pylori: Neurological and Ophthalmological Disorders. The Internet Journal of Neurology. 2008 Volume 9 Number 2.
http://www.ispub.com/journal/the-internet-journal-of-neurology/volume-9-number-2/helicobacter-pylori-neurological-and-ophthalmological-disorders.html

[v] J. Kountouras, C. Zavos, et al. Helicobacter pylori might be a potential therapeutic target in epilepsy. Med Hypotheses. 2011 May;76(5):763. Epub 2011 Feb 26, p. 736.

[vi] A. Ozturk, C.E. Ozturk, et al. Helicobacter pylori infection in epileptic patients. Seizure. 2007 (16), pp. 147-152.

[vii] M. Okuda, E. Miyashiro, et al. Helicobacter pylori infection and idiopathic epilepsy. Am J Med. 2004 Feb 1;116(3):209-10, p. 209.

[viii] K.E. Quesenberry, J.W. Carpenter. Ferrets, Rabbits, and Rodents: Clinical Medicine and Surgery. St. Louis, Missouri, Elsevier Inc., 2011.

APPENDIX

STUDY TYPE: Pilot Companion Animal Safety Study - Pediatric Ferrets; Non-guideline.

TEST MATERIAL (PURITY): M880 Insecticide [9.1% (w/v) Imidacloprid and 0.46% (w/v) Pyriproxyfen; Lot No. KP06T8L KP06 SOR]

SYNONYMS: Advantage® II Small Cat

CITATIONS: Madsen, T. (2012) Pilot general safety evaluation of M880 Insecticide on pediatric ferrets. Sinclair Research Center, LLC (SRC), Auxvasse, Missouri. Study Number S10986A, April 25, 2012. MRID 48880901. Unpublished.

SPONSOR: Bayer HealthCare LLC / Animal Health Division, 12809 Shawnee Mission Parkway, Shawnee Mission, Kansas.

EXECUTIVE SUMMARY: A two-phase pilot companion animal safety study (MRID 48880901) preliminarily evaluated the safety of M880 Insecticide [9.1% (w/v) Imidacloprid and 0.46% (w/v) Pyriproxyfen; Lot No. KP06T8L KP06 SOR] in pediatric ferrets. In Phase 1, the test material was applied topically to groups of three male and three female ferrets that were 8-, 12-, or 16-weeks-old (±2 days) at total dosing volumes of 2.0 mL/animal, i.e., 5X the intended label-recommended dosing volume. Mineral oil or M880 Insecticide Placebo (the final formulation minus the active ingredients) were applied to two additional (control) groups of two male and two female 8-week-old ferrets at total dosing volumes of either 2.0 mL/animal (mineral oil) or 1.8 mL/animal (M880 Insecticide Placebo, to give inert ingredients at the maximum levels that would appear in the 5X formulation). In Phase 2, a group of five male and three female 10-week-old (±1 day) ferrets were treated with M880 Insecticide Placebo at a total volume of 1.8 mL/animal, i.e., 5X the intended label-recommended dosing volume of the inert ingredients. In both phases, the test material or vehicle was applied to the interscapular region of each animal via calibrated pipette or via the polypropylene tube in which the test material was packaged, with the total dosing volume achieved through five equally sized "sub-applications" that were either 0.4 mL or 0.36 mL apiece, as appropriate, and given at 60-minute intervals. Treatment was on day 0, and the animals were observed for up to four days with the routinely evaluated parameters including body weight, food consumption, and hematology/clinical chemistry. The second phase was added to the study due to deaths of two 8-week-old 5X vehicle control ferrets during Phase 1.

During the post-treatment observations on day 0, all study animals were observed to have matted, greasy, and/or spiked hair at the dose site, i.e., from the base of the head to the interscapular region. Additional findings were as follows.

Phase 1:

8-week-old negative controls: Two/four animals had persistence of the greasy hair coat in the interscapular region through day 1, and 1/4 had feces that were partly mucoid on day 2. One male failed to gain weight.

8-week-old vehicle controls: One female (#297) was found dead at the initial day 1 observation; a male (#186) died on day 1 after exhibiting lethargy, weakness, and pawing at the mouth. One/2

survivors had feces that were partly mucoid (on day 2). Both decedents were subjected to full necropsy, including collection of blood, urine, and selected tissues. Clinical pathology findings included changes in serum electrolytes, total protein, blood glucose, AST, ALT, ALP, and BUN (compared to pre-test values), and moderate to high numbers of granular casts were noted in the urine. Histopathology in both animals included suppurative cholangitis, mild enteritis characterized grossly by reddened gastrointestinal contents, and mesenteric lymph node enlargement, and the male also had submucosal hemorrhage of the gallbladder and myocardial edema. There were no histopathological correlates to the elevated ALT and AST activities; however, marked increased ALP activity is suggestive of biliary stasis, which would be consistent with the finding of cholangitis. The increased BUN together with the granular casts observed in the urine may indicate early renal dysfunction or inflammation, but there were no histopathological correlates. The underlying cause of the histologic lesions was not clear from microscopic examination. According to the pathology report, the gross finding of hemorrhage within the gastrointestinal tracts of both animals was most likely associated with *Helicobacter mustelae* infection as manifested by hemorrhagic gastritis, and the most likely cause of the acute deaths of both animals was hemorrhagic or ulcerative gastritis related to *Helicobacter mustelae* infection. The organism was not confirmed in these animals via post-mortem testing, but the pathologist stated that the clinical presentation and gross necropsy findings were consistent with research literature and that *H. mustelae* is present endemically at the animal supplier. The supplier also noted that increases in juvenile ferret mortality are intermittently observed in their colony. The pathologist also mentioned that acute deaths with pathologic evidence of hemorrhagic gastritis associated with the detection of Helicobacter (including microscopic identification) were noted in 5 of 93 ferrets purchased for acclimation and study use by the CRO from this supplier in the months following these study events. The pathologist also noted that a potential relationship to treatment could not be ruled out.

8-week-old 5X animals: One/6 had feces that were partly mucoid and with areas of red coloration (on day 1). One male lost weight (37.1 g during days -1 to 4).

12-week-old and 16-week-old 5X animals: No deaths or abnormal clinical signs, and all animals gained weight.

Phase 2:

10-week-old vehicle controls: No deaths or abnormal clinical signs, and all animals gained weight.

Based on the results of this study, 10-week-old ferrets were used in the definitive companion animal safety study.

COMPLIANCE: Signed and dated GLP and Data Confidentiality statements were provided; according to the GLP statement, this pilot study was *not* conducted in compliance with the GLP regulations set forth in 40 CFR Part 160.

EFFICACY REVIEW

PRODUCT: Advantage II Small Cat

DATE: August 29, 2012

FILE SYMBOL: 11556-151

DP BARCODE: 404200

DECISION: 466880

GLP: No

CHEMICALS: Imidacloprid (9.1%) + Pyriproxyfen (.46%)

CHEMICAL NUMBERS: Imidacloprid – 129099 Pyriproxyfen – 129032

PURPOSE: To add ferrets to the label and the control of fleas on ferrets

MRID: 48880903. Laboratory Evaluation of the Efficacy of Advantage II for Small Cats (9.1% Imidacloprid + 0.46% Pyriproxyfen) for the Treatment and Control of Cat Fleas (*Ctenocephalides felis*) on Ferrets

TEAM REVIEWER: Autumn Metzger

EFFICACY REVIEWER: Autumn Metzger, M.S. 8/29/12

SECONDARY EFFICACY REVIEWER: Jennifer Urbanski, Ph.D. 8/29/12

BACKGROUND

Advantage II Small Cat is a topical spot-on insecticide treatment for the control of fleas on small cats and kittens 8 weeks and older and 5 to 9 lbs. The product is applied on the skin between the shoulder blades once monthly. The directions for ferrets will be to use the same size pipette used for small cats (0.014 fl. oz/ 0.4 ml) on ferrets 10 weeks and older and 1lb or greater.

DATA REVIEW

The following data review is comprised of explanations of materials and methods, and a summation of experimental results containing tables with reformatted data.

MRID: 48880903. Laboratory Evaluation of the Efficacy of Advantage II for Small Cats (9.1% Imidacloprid + 0.46% Pyriproxyfen) for the Treatment and Control of Cat Fleas (*Ctenocephalides felis*) on Ferrets

Objective

To evaluate the effectiveness of Advantage II Small Cat against fleas on ferrets 1 lb and greater.

GLP: No

Set Up
Sixteen ferrets were split into 2 groups of 8:

Group 1 = untreated /negative control
Group 2 = treated with 1 dose of Advantage II for Small Cats

Ferrets ages ranged from 26.6-42 weeks old. There were 8 neutered females, 4 intact males and 4 neutered males included in the study. Males weighed from 1.16-1.54 kg and females weighed .72-.84 kg giving doses that ranged from 25.9-55.4 mg imidacloprid/kg and 1.3-2.8 mg pyriproxyfen/kg.

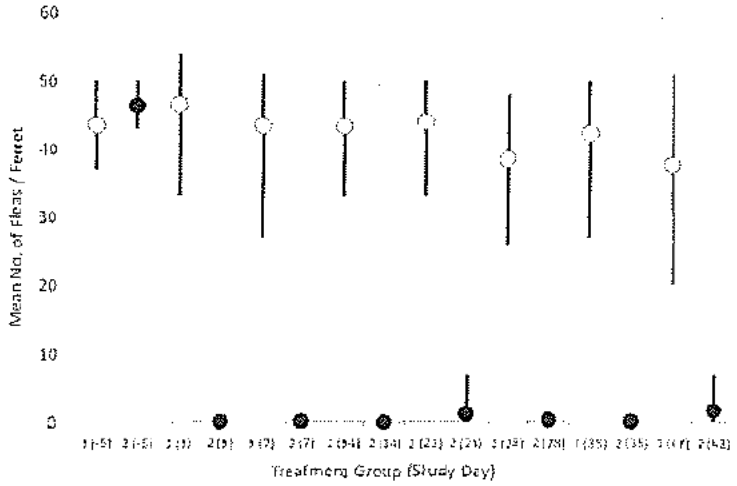
The ferrets were housed in individual cages and treated on day zero. They were infested with ~50 cat fleas on days -1, 5, 12, 9, 26, 33 & 40. Fleas were counted and collected 24 hours after the first infestation and 48 hours after each other infestation.

Results

Efficacy/flea mortality was at 100% on day 1 and efficacy stayed above 97.5% on all counts vs. the untreated control. Efficacy did not appear to be influenced by ferret size, sex or whether it had been neutered.

16. Figures

Figure 1. Geometric mean number of cat fleas per ferret for each treatment group on each study day. Open circles (o) are means for Group 1 (controls); solid circles (•) are means for Group 2 (*Advantage II*). Bars represent the range of counts.



Adverse effects were seen on 3 ferrets. Effects included 2 semi-formed feces in control/untreated ferrets and 1 incidence of diarrhea in a treated ferret. All of the effects occurred on day zero post-treatment.

Conclusion

The product and the dose used is sufficient to allow the claim that Advantage II Small Cat will control and prevent against flea infestations on ferrets (1 lb and greater) for up to 40 days.

RECOMMENDATIONS:

<u>Revise the following claims:</u>

Page 5:

- *"Advantage® II Small Cat kills the existing fleas on ferrets within 12 hours. Reinfesting fleas are killed within 2 hours with protection against further flea infestation lasting for up to four (4) weeks. Pre-existing pupae in the environment may continue to emerge for six (6) weeks or longer depending upon the climatic conditions"* **to read:** *"Advantage® II Small Cat kills the existing fleas on ferrets within 24 hours. Reinfesting fleas are killed with protection against further flea infestation lasting for up to four (4) weeks. Pre-existing pupae in the environment may continue to emerge for six (6) weeks or longer depending upon the climatic conditions."* **The shortest time period tested on ferrets was 24 hours. Bridging the time periods from the cat product will not be accepted.**

- *"Advantage® II Small Cat kills adult fleas quickly, within 12 hours, inhibits the development of immature flea life stages and prevents them from reaching the biting adult stage"* **to read:** *"Advantage® II Small Cat kills adult fleas within 24 hours, inhibits the development of immature flea life stages and prevents them from reaching the biting adult stage."* **The shortest time period tested on ferrets was 24 hours, which is also not considered "quickly." Bridging the time periods from the cat product will not be accepted.**

Pg 7:

- *"Kills fleas within [12] hours and continues to prevent infestations for up to [four weeks] [a month]"* **to read:** *"Kills fleas within 12 hours on cats and continues to prevent infestations for up to [four weeks] [a month]"* **or** *"Kills fleas within 12 hours on cats and 24 hours on ferrets and continues to prevent infestations for up to [four weeks] [a month]"* **The shortest time period tested on ferrets was 24 hours. Bridging the time periods from the cat product will not be accepted. In addition, using brackets is not acceptable as it could be misleading if the bracketed part was deleted and it said "kills fleas in hours."**

- "Kills fleas within [12] hours of application" **to read:** "Kills fleas on cats within 12 hours of application" **or** "Kills fleas on cats within 12 hours and on ferrets within 24 hours of application." **The shortest time period tested was 24 hours. Bridging the time periods from the cat product will not be accepted. In addition, using brackets is not acceptable as it could be misleading if the bracketed part was deleted and it said "kills fleas in hours."**

- *"Reinfesting fleas are killed within 2 hours with protection against further flea infestation"* **to read:** *"Reinfesting fleas are killed on cats within 2 hours with protection against further flea infestation."* **The shortest time period tested for ferrets was 24 hours.**

All other added claims are acceptable (from an efficacy standpoint) based on the data provided or can be bridged from the existing cat claims (i.e. waterproof, bathing, flea eggs/life cycle/larvae type claims).

11/8/2012

NOTE TO FILE:

When the PM beaned the Companion Animal Study to TRB, attached to it was MRIDs for efficacy. TRB sent all of the MRIDs out to a contractor to be reviewed. Therefore, the contractor reviewed the efficacy studies even though the efficacy team (A. Metzger) had already reviewed it. The conclusions were the same. The DER from the contractor is included in this jacket (dated 9/12/2012).

Autumn Metzger

TASK 2 DATA EVALUATION RECORD

STUDY TYPE: Product Performance

MRID 488809-03. McCall, J.W. and D.H. Ross. 2011. Laboratory Evaluation of the Efficacy of *Advantage II for Small Cats* (9.1% Imidacloprid + 0.46% Pyriproxyfen) for the Treatment and Control of Cat Fleas (*Ctenocephalides felis*) on Ferrets.

Treatments to Control Pests of Humans and Pets (810.3300)

Product Name: *Advantage II for Small Cats*
EPA Reg. No. or File Symbol: 11556-151
Decision number: 466880
DP number: 404120

Prepared for
Registration Division (7505)
Office of Pesticide Programs
U.S. Environmental Protection Agency
Washington, DC20460

Prepared by
Summitec Corporation
Task Order No.: 3-C-11

Primary Reviewer:
Dennis M. Opresko, Ph.D.

Signature: [signature]
Date: SEP 19 2012

Secondary Reviewers:
Robert H. Ross, M.S.

Signature: Robert H. Ross
Date: SEP 19 2012

Robert H. Ross, M.S. Program Manager

Signature: Robert H. Ross
Date: SEP 19 2012

Quality Assurance:
Angela Edmonds, B.S.

Signature: Angela Edmonds
Date: SEP 19 2012

Disclaimer

This review may have been altered subsequent to the contractors' signatures above.

DATA EVALUATION RECORD

[EPA Primary Reviewer's Name]

STUDY TYPE:	Treatments to Control Pests of Humans and Pets (810.3300)
MRID:	488809-03. Laboratory Evaluation of the Efficacy of *Advantage II for Small Cats* (9.1% Imidacloprid + 0.46% Pyriproxyfen) for the Treatment and Control of Cat Fleas (*Ctenocephalides felis*) on Ferrets. McCall, J.W. and D.H. Ross. Sept. 23, 2011.
DP BARCODE:	404120
DECISION NO:	466880
SUBMISSION NO:	919516
SPONSOR:	Bayer HealthCare, LLC. P.O. Box 390 Shawnee Mission, KS 66201-0390
TESTING FACILITY:	TRS Labs, Inc. 295 Research Drive Athens, GA 30605
STUDY DIRECTOR:	John W, McCall, Ph.D., TRS Labs, Inc.
SUBMITTER:	Douglas A. Spilker Bayer HealthCare, Inc.
STUDY COMPLETED:	23/09/2011
CONFIDENTIALITY CLAIMS:	None
GOOD LABORATORY PRACTICE:	"The study was conducted in compliance with Good Clinical Practiced (GCP) based on VICH GL9 and record keeping as outlined in the protocol. This study was not conducted in full compliance with Good Laboratory Practice standards (e.g., U.S. Environmental Protection Agency; Federal Insecticide, Fungicide and Rodenticide Act [FIFRA], 40 CFR Part 160)."

TEST MATERIAL:	PRODUCT NAME: Advantage® II Small Cat EPA REGISTRATION NUMBER OR FILE SYMBOL: 11556-151 ACTIVE INGREDIENT NAMES: Imidacloprid + Pyriproxyfen. CHEMICAL NAME: NA A.I. %: Imidacloprid 9.10%; + Pyriproxyfen 0.46%. PC CODE: Imidacloprid 129032; Pyriproxyfen 129099 CAS NO.: Not given FORMULATION TYPE: Spot-on PRODUCT APPLICATION RATE(S): One tube (0.4 mL) per application; once a month. ACTIVE INGREDIENT APPLICATION RATE(S) g/m^2: Not specified.
PROPOSED LABEL MARKETING CLAIMS:	…kills the existing fleas on ferrets within 12 hour. Reinfesting fleas are killed within 2 hours with protection from further flea infestation lasting up to four (4) weeks…

STUDY REVIEW

Purpose: To evaluate the efficacy of "*Advantage® II Small Cat*" against cat fleas on ferrets (*Mustela putorius furo*). The study was also designed to evaluate the effect differences in body size/weight on efficacy.

MATERIALS AND METHODS

Test Location: Athens, GA (TRS Labs, Inc.)

Test Material(s): *Advantage® II Small Cat* (9.10% imidacloprid and 0.46% pyriproxyifen). Test material was identical to the product listed under EPA No. 11556-151.

Test Species Name, Life Stage, Sex and Age: Cat flea (*Ctenocephalides felis*). Adults were tested.

Describe test containers, chambers and/or apparatus (include site description and location) and how experiment was conducted: Tests were conducted on ferrets; 26.6-42 weeks-old prior to the start of the tests (4 intact males, 4 neutered males; and 8 neutered females). Male ferrets weighed 1.16-1.54 kg; females weighed 0.72-0.84 kg. The test animals were evaluated for their susceptibility to flea infestation before the study began. They were then randomly assigned to one of two groups. One group of eight ferrets was treated with the test product on SD 0 according to label directions. A second group of eight ferrets served as the untreated control group. The test animals were housed in individual cages with partitions to prevent animal-to-animal contact. Both groups were infested with approximately 50 adult unfed fleas on SD's -1, 5, 12, 19, 26, 33, and 40. On SD 0, ferrets were observed at 1, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-treatment, and then once

daily thereafter. Fleas were counted and removed from all ferrets on SD 1, approximately 24 hours after treatment, and on SD's 7, 14, 21, 28, 35, and 42, approximately 48 hours after flea infestation.

List the treatments including untreated control (express application rate as g/m^2): One application (0.4 mL) per animal. Controls were not treated.

Number of replicates per treatment: 1.

Number of individuals per replicate: 8.

Length of exposure to treatment (time in seconds, minutes or hours): Single application of 1 tube (0.4 mL) per animal.

Were tested specimens transferred to clean containers? NA.

Experimental conditions (state relative humidity, temperature, and photoperiod): Not reported.

Data or endpoints collected/recorded: Number of fleas present at each observation time.

Data analysis:

Efficacy of the IVP, relative to the control group, was computed with Abbott's formula using geometric means.

$$\% \text{ Efficacy} = 100 \times \frac{(\text{Geo. mean flea count}_{(\text{Control})} - \text{Geo. mean flea count}_{(\text{Treatment})})}{\text{Geo. mean flea count}_{(\text{Control})}}$$

Geometric means were calculated following transformation using a logarithmic method (averaging the transformed values, and converting the average using antilog to represent a geometric mean). Because some animals had zero (0) counts, all counts were modified by adding one (1) to each prior to logarithmic transformation. Also, one (1) was subtracted from the antilog value to meaningfully represent the geometric mean for each group.

Log (counts+1) were analyzed with a repeated measures analysis of covariance (RMANCOVA) including terms for treatment (TRT), animal (random), study day (DAY), and the interaction of treatment and study day (TRT x DAY), using the pre-treatment counts as a covariate. SAS PROC MIXED (SAS® Institute, Cary, NC) was used for analysis with the covariance structures 'AR(1)' and 'ARH(1)' for data collected on equal intervals, or 'CS' and 'CSH' for data collected on unequal intervals. Results from the model with the smallest Akaike's Information Criterion were used.

If the interaction of treatment and study day was significant at the 0.05 level, the active treatment group was compared to the control through the simple effect of TRT for each time point. These simple effect pairwise comparisons were obtained from the TRT x DAY interaction. If the interaction term was not significant ($p > 0.05$), the TRT main effect was evaluated. If the TRT main effect was not significant ($p > 0.05$), the results were deemed not significant and no further analyses were conducted. If the TRT main effect was significant ($p <= 0.05$), linear contrasts were constructed for pairwise comparison of the active treatment group with the control across the pooled time points.

RESULTS

Raw data were not included in the study report. The only protocol deviation reported involved three adverse events (abnormal feces) that were not reported within 5 days to the sponsor). These events, two of which occurred in control animals) were not considered to have an impact on the outcome of the study.

Mean number of fleas found in the treated and control groups are shown in Table 1.

Table 1. Geometric mean numbers of live cat fleas for the *Advantage II* (treated) and untreated control groups. For each study day, means followed by different letters indicate a significant difference in flea counts ($p < 0.0001$) between the groups.

Study Day	Treatment	Mean # cat fleas/ferret	
1	*Advantage II*	0	*a*
	Control	45.9	*b*
7	*Advantage II*	0	*a*
	Control	42.6	*b*
14	*Advantage II*	0	*a*
	Control	43.0	*b*
21	*Advantage II*	0.5	*a*
	Control	43.5	*b*
28	*Advantage II*	0.2	*a*
	Control	37.8	*b*
35	*Advantage II*	0	*a*
	Control	41.4	*b*
42	*Advantage II*	0.9	*a*
	Control	35.9	*b*

The imidacloprid and pyriproxyfen dosages per unit body weight for each treated animals are shown in Table 2.

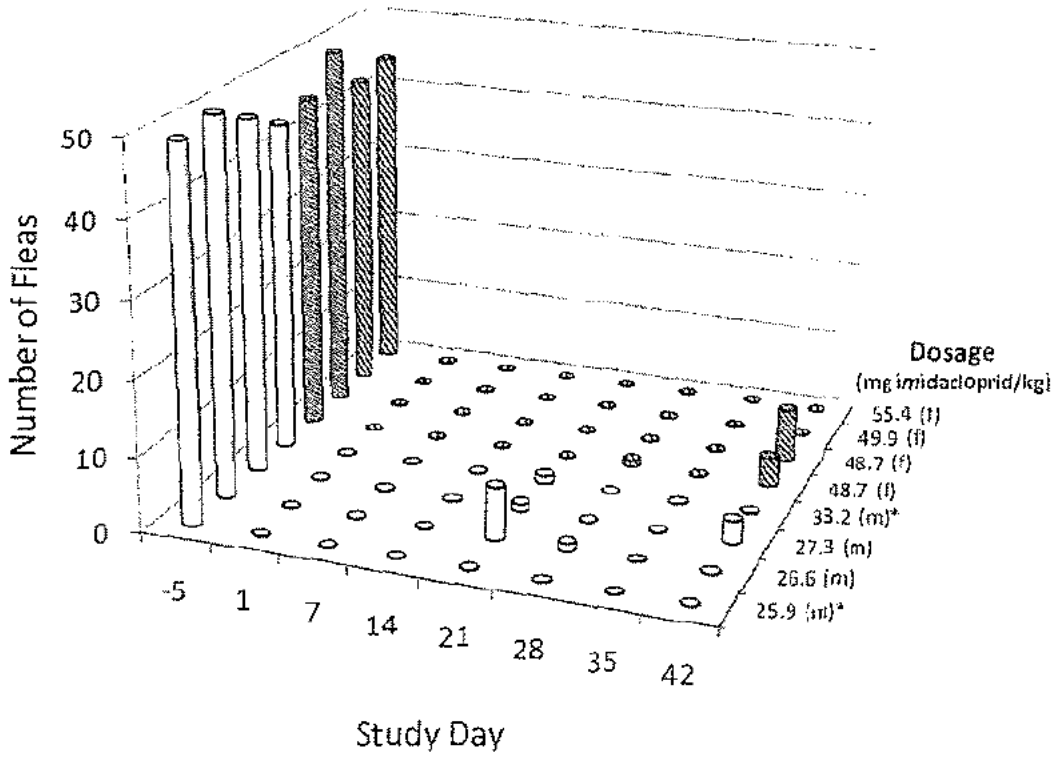
Table 2. Body weights of individual ferrets treated with *Advantage II for Small Cats*, and calculations of the dosage (mg/kg body weight) of both active ingredients applied to each animal.

			Advantage II for Small Cats		imidacloprid (9.1%)		pyriproxyfen (0.46%)	
Animal ID	Gender	Body Weight (kg)	Dose Volume (mL)	Specific Gravity	mg/0.4 mL dose	Dosage mg/kg body weight	mg/0.4 mL dose	Dosage mg/kg body weight
104	F	0.72				55.4		2.8
379	F	0.80				49.9		2.5
858	F	0.82				48.7		2.5
576	F	0.82	0.4	1.096	39.89	48.7	2.02	2.5
325	M*	1.20				33.2		1.7
789	M	1.46				27.3		1.4
351	M	1.50				26.6		1.3
81	M*	1.54				25.9		1.3

*Intact male

The number of cat fleas present on each treated ferret arranged by imidacloprid dose is shown in the following figure.

Number of cat fleas on ferrets in Group 2 (*Advantage II*) on each study day. Data are ordered by imidacloprid dosage (mg/kg), which is inversely proportional to body weight. [(f) = neutered female; (m) = neutered male; (m)* = intact male]



Study Author's Conclusions

The test substance demonstrated excellent initial and residual efficacy against cat fleas on ferrets, ranging from 97.5%-100% for 42 days post-treatment. Body weight of the test animal had no impact on efficacy.

Reviewer's Conclusions

Study results support the conclusions of the study author. Under the conditions of the test "*Advantage® II Small Cat*" effectively controlled cat fleas on ferrets for up to 42 days. Flea counts on treated animals were lower by 97.5% or more compared to untreated animals for all time periods for animals weighing up to 1.54 kg.

Reviewer's Recommendations

Study supports the addition of ferrets weighing up to 1.54 kg to the product label.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

July 12, 2012

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

BAYER HEALTHCARE LLC
PO.BOX : 390
SHAWNEE MISSION, KS 66201-0390

Report of Analysis for Compliance with PR Notice 11-03

Thank you for your submittal of 29-JUN-12. Our staff has completed a preliminary analysis of the material. The results are provided as follows:

Your submittal was found to be in full compliance with the standards for submission of data contained in PR Notice 11-03. A copy of your bibliography is enclosed, annotated with Master Record ID's (MRIDs) assigned to each document submitted. Please use these numbers in all future references to these documents. Thank you for your cooperation. If you have any questions concerning this data submission, please raise them with the cognizant Product Manager, to whom the data have been released.

PRIA 2 – 21 Day Content Screen Review Worksheet

(EPA/OPP Use Only)

3/23/09

21 Day Screen Start Date: 6-25-12

Experts In-Processing Signature: MF Hannaman Date 7-6-12 Fee Paid: Yes ✓

Division management contacted on issues No_____Yes _____Date _____

EPA Reg. Number: 11556-151	EPA Receipt Date: 6-29-12

	Items for Review			Yes	No	N/A*
1	**Application Form** (EPA Form 8570-1)(link to form) signed & complete including package type			X		
2	**Confidential Statement of Formula** all boxes completed, form signed, and dated (EPA Form 8570-4) (Link to form)					X
	a) All inerts (link to http://www.epa.gov/opprd001/inerts/), including fragrances, approved for the proposed uses (see Footnote A)	**yes**	**no**			
3	**Certification with Respect to Citation of Data** (EPA Form 8570-34) (Link to form) completed and signed (N/A if 100% repack)			X		
	Certificate and data matrix consistent			X		
	If applicant is relying on data that are compensable, is the offer to pay statement included. (see Footnote B)	**yes**	**no**			
	If applicable, is there a letter of Authorization for exclusive use only.					
4	**Formulator's Exemption Statement** (EPA Form 8570-27) (Link to form) completed and signed (N/A if source is unregistered or applicant owns the technical)					X
5	**Data Matrix** (EPA Form 8570-35) (Link to form) both internal and external copies (PR 98-5) (Link to PR 98-5) completed and signed (N/A if 100% repack)			X		
	a) Selective Method (Fee category experts use)	**yes** X	**no**			
	b) Cite-All (Fee category experts use)					
	c) Applicant owns all data (Fee category experts use)					
6	**5 Copies of Label (link to http://www.epa.gov/oppfead1/labeling/lrm/) (Electronic labels on CD are encouraged and guidance is available)(link to** http://www.epa.gov/pesticides/regulating/registering/submissions/index.htm#labels)			X		

7	**Is the data package consistent with PR Notice 86-5** (link to PRN 86-5)	X		
8	**Notice of Filing (link to http://www.epa.gov/pesticides/regulating/tolerance_petitions.htm) included with petitions (link to http://www.epa.gov/pesticides/regulating/tolerances.htm)**			X
9	**If applicable for conventional applications, reduced risk rationale (link to http://www.epa.gov/opprd001/workplan/reducedrisk.html)**			X
10	**Required Data (link to http://www.epa.gov/pesticides/regulating/data_requirements.htm) and/or data waivers. See Footnote C.**			
	a) List study (or studies) not included with application			

7	**Is the data package consistent with PR Notice 86-5** (link to PRN 86-5)	X		
8	**Notice of Filing (link to http://www.epa.gov/pesticides/regulating/tolerance_petitions.htm) included with petitions (link to http://www.epa.gov/pesticides/regulating/tolerances.htm)**			X
9	**If applicable for conventional applications, reduced risk rationale (link to http://www.epa.gov/opprd001/workplan/reducedrisk.html)**			X
10	**Required Data (link to http://www.epa.gov/pesticides/regulating/data_requirements.htm) and/or data waivers. See Footnote C.**			
	a) List study (or studies) not included with application			

Comments:

Studies associated with this submission passed PRN-11-03 review.

- Regarding the application package, certification with Respect to citation of Data and Data Matrix was missing. Registrant was contacted on 07/12 and corrections were received on the same day.

PRN-11-03 review - Passed

Amendment - Passed

J.S/ 07-13-12 MRID-488809

* N/A – Not Applicable

Footnotes

A. During the 21 day initial content review, all CSFs will be reviewed to determine whether all inerts listed, including fragrances, are approved for the proposed uses. If an unapproved inert is identified, the applicant must either 1) resolve the inert issue by, for example, removing the inert, substituting it with an approved inert, submitting documentation that EPA approved the inert for the proposed pesticidal uses, correcting mistakes on the CSF, etc. or 2) provide the data to support OPP approval of the inert or 3) withdraw the application. Removing or substituting an inert ingredient will require a new CSF and may require submission of data. All information, forms, data and documentation resolving the inert issue must have been received by the Agency or the application withdrawn within the 21 day period, otherwise, the Agency will reject the application as described below.

To successfully complete this aspect of the 21 day initial content screen, applicants are **strongly encouraged** to verify that all inert ingredients have been approved for the application's uses **even if a product is currently registered** by consulting the inert Web

Script for Rejection Phone calls

Contact Name: Doug Spiker
Phone #: 919-268-2751
Email: doug.spiker@bayer.com

Planned

First Call/Initials:	**Second Call/Initials:**
Date: 12/12/12	**Date:** 07/12/12
Time: 8:30 am	**Time:** 12:15 pm

This is Srijana Shrestha**, EPA contractor.**

I'm calling regarding your submission in support of
EPA Reg# 11556-151.

We have found the following deficiencies regarding:
PR Notice 2011-3: Yes or (No)
Volume/Study Title:

Volume/Study Title:

Volume/Study Title:

Additional volumes continued on back of page: Yes or No

Application Package: (Yes) or No
Certification form & Data matrix is missing.

These deficiencies have been approved by EPA.
The corrections can be faxed to 703-305-5060/Attn: _____.

Second Call/Email:
If we do not receive the corrections by _____, we will process your submission, accordingly. Please direct all future calls and correspondence to the appropriate EPA Risk Manager.

RE: Submission in support of the product, "Advantage II Small Cat" (EPA Reg# 11556-151)
Doug Spilker
to:
Srijana Shrestha
07/12/2012 11:28 AM
Cc:
Sree Nair
Hide Details
From: Doug Spilker <doug.spilker@bayer.com>

To: Srijana Shrestha/DC/USEPA/US@EPA

Cc: Sree Nair/DC/USEPA/US@EPA

3 Attachments

image001.gif Adv II 8570-34 July 2012.pdf Adv II Cats DM Conf July 2012.pdf

Dear Ms. Shrestha,

Please find attached the required EPA Form 8570-34 and the Data Matrix of the data that supports this product, as well as supports the other two cat products (which are the exact same formulation).

The Public version of the Data Matrix will be sent in a separate email.

We apologize for any inconvenience.

Best Regards,
Doug

Douglas A. Spilker, Ph.D.
Manager - EPA Reg. Affairs
BAYER HEALTHCARE LLC
Animal Health Division
Office: 913-268-27S1
Mobile: 816-506-3102

RE: Submission in support of the product, "Advantage II Small Cat" (EPA Reg# 11556-151)
Doug Spilker
to:
Srijana Shrestha
07/12/2012 11:30 AM
Cc:
Sree Nair
Hide Details
From: Doug Spilker <doug.spilker@bayer.com>

To: Srijana Shrestha/DC/USEPA/US@EPA

Cc: Sree Nair/DC/USEPA/US@EPA

2 Attachments

image001.gif Adv II Cats DM Public July 2012.pdf

Dear Ms. Shrestha,

Please find attached the Public version of the Data Matrix. Please let us know if you need anything further.

Best Regards,
Doug

Douglas A. Spilker, Ph.D.
Manager - EPA Reg. Affairs
BAYER HEALTHCARE LLC
Animal Health Division
Office: 913-268-2751
Mobile: 816-506-3102
Email: doug.spilker@bayer.com

Address:
P.O. Box 390
Shawnee Mission, KS 66201-0390

Country: USA

Bayer Animal Health "Protecting.Curing.Caring...Together"

From: Srijana Shrestha [mailto:Shrestha.Srijana@epamail.epa.gov]
Sent: Thursday, July 12, 2012 9:45 AM
To: Doug Spilker
Cc: Sree Nair
Subject: RE: Submission in support of the product, "Advantage II Small Cat" (EPA Reg# 11556-1S1)

Dear Mr. Spilker:

Yes, we will require both the Public and Agency (Confidential) Copy of Data Matrices.

Thank you,

Srijana Shrestha
Macfadden, EPA Contractor
2777 S. Crystal Drive, S 4910 A
Arlington, VA 22202
Ph: 703-305-6471
Fax: 703-305-5060

Doug Spilker ---07/12/2012 10:14:34 AM---Dear Ms. Shrestha, Thank you for your message. Thank you also for the clarification on why these for

From: Doug Spilker <doug.spilker@bayer.com>
To: Srijana Shrestha/DC/USEPA/US@EPA
Date: 07/12/2012 10:14 AM
Subject: RE: Submission in support of the product, "Advantage II Small Cat" (EPA Reg# 11556-1S1)

Dear Ms. Shrestha,

Thank you for your message. Thank you also for the clarification on why these forms are required. I did not previously understand that an amendment required these documents. I will update them as soon as possible and get them to you. I assume that you need both the Public and Confidential Data Matrices. Would you please confirm this?

Best Regards,
Doug

Douglas A. Spilker, Ph.D.
Manager - EPA Reg. Affairs
BAYER HEALTHCARE LLC
Animal Health Division
Office: 913-268-2751
Mobile: 816-506-3102
Email: doug.spilker@bayer.com

Address:
P.O. Box 390
Shawnee Mission, KS 66201-0390

Country: USA

Bayer Animal Health "Protecting.Curing.Caring...Together"

From: Srijana Shrestha [mailto:Shrestha.Srijana@epamail.epa.gov]
Sent: Thursday, July 12, 2012 8:45 AM
To: Doug Spilker
Cc: Sree Nair
Subject: Submission in support of the product, "Advantage II Small Cat" (EPA Reg# 115S6-1S1)

Dear Mr. Spilker:

This is regarding your submission in support of the product, "Advantage II Small Cat" (EPA Reg# 11556-151). We have found following issues with with your submission:

t) Certification with Respect to Citation of Data (EPA Form 8570-34): It is required for review process, since there are studies associated.

2) Data Matrix (EPA Form 8570-35): It is also required for review process, since there are studies associated with it

Please send the missing forms by email. I left a VM as well regarding the issues. Feel free to call me back at 703-305-6471, if you have any questions.

Thanking you,

Srijana Shrestha
Macfadden, EPA Contractor
2777 S. Crystal Drive, S 4910 A
Arlington, VA 22202
Ph: 703-305-6471
Fax: 703-305-5060

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

July 6, 2012

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

OPP Decision Number: D-466880
EPA File Symbol or Registration Number: 11556-151
Product Name: ADVANTAGE II SMALL CAT
EPA Receipt Date: 29-Jun-2012
EPA Company Number: 11556
Company Name: BAYER HEALTHCARE LLC

DR. BRUCE MARTIN
BAYER HEALTHCARE LLC
ANIMAL HEALTH DIVISION
PO Box 390
SHAWNEE MISSION, KS 66201-0390

SUBJECT: Receipt of Registration Amendment Subject to Registration Service Fee

Dear Registrant:

The Office of Pesticide Programs has received your amendment and certification of payment. If you submitted data with this application, the results of the PRN-2011-3 screen will be communicated separately. During the administrative screen, the Office of Pesticide Programs has determined that this Action is subject to a Pesticide Registration Service Fee as defined in the Pesticide Registration Improvement Act.

The Action has been identified as Action Code: R340

NON-FAST-TRACK (INCLUDES CHANGES TO PRECAUTIONARY LABEL STATEMENTS;SOURCE CHANGES TO AN UNREGISTERED SOURCE);

No additional payment is due at this time.

If you have any questions, please contact the Pesticide Registration Service Fee Ombudsman at (703) 308-9362.

Sincerely,
Teresa Downs
Front End Processing Staff
Information Technology & Resources Management Division

Fee for Service {9195167~

This package includes the following

- ○ New Registration
- ◉ Amendment

☐ Studies? ☐ Fee Waiver?

☐ volpay % Reduction: ___

for Division

- ○ AD
- ○ BPPD
- ◉ RD

Risk Mgr. 10

Receipt No. S- 919516

EPA File Symbol/Reg. No. 11556-151

Pin-Punch Date: 6/29/2012

☐ This item is NOT subject to FFS action.

Action Code:

Requested: R340

Granted: R340

Amount Due: $ 3,617.00

Parent/Child Decisions:

☐ Inert Cleared for ~~Intended Use~~ ☐ Uncleared Inert in Product

Reviewer: _____ Date: 7-3-12

Remarks:

Online Payment

Step 3: Confirm Payment 1 | 2 | **3**

Thank you.
Your transaction has been successfully completed.

Pay.gov Tracking Information

Application Name: PRIA Service Fees
Pay.gov Tracking ID: 2574LG80
Agency Tracking ID: 74327965953
Transaction Date and Time: 06/26/2012 08:21 EDT

Payment Summary

Address Information

Account Holder Name: Douglas A Spilker
Billing Address: 12707 Shawnee Mission Parkway
Billing Address 2:
City: Shawnee
State / Province: KS
Zip / Postal Code: 66216-1846
Country: USA

Account Information

Card Type: Master Card
Card Number: **********0576
Decision Number:
Registration Number: 11556-151
Company Name: Bayer HealthCare LLC-AH
Company Number: 11556
Action Code: R340

Payment Information

Payment Amount: $3,617.00
Transaction Date and Time: 06/26/2012 08:21 EDT

Doug Spilker

From: paygovadmin@mail.doc.twai.gov
Sent: Tuesday, June 26, 2012 7:21 AM
To: Doug Spilker
Subject: Pay.gov Payment Confirmation: PRIA Service Fees

Your payment has been submitted to Pay.gov and the details are below. If you have any questions regarding this payment, please contact Pay.gov Customer Service by phone at (800) 624-1373 or by email at pay.gov.clev@clev.frb.org.

Application Name: PRIA Service Fees
Pay.gov Tracking ID: 2574LG80
Agency Tracking ID: 74327965953
Transaction Type: Sale
Transaction Date: Jun 26, 2012 8:21:29 AM

Account Holder Name: Douglas A Spilker
Transaction Amount: $3,617.00
Billing Address: 12707 Shawnee Mission Parkway
City: Shawnee
State/Province: KS
Zip/Postal Code: 662161846
Country: USA
Card Type: MasterCard
Card Number: **********0576

Decision Number:
Registration Number: 11S56-1S1
Company Name: Bayer HealthCare LLC-AH
Company Number: 11556
Action Code: R340

THIS IS AN AUTOMATED MESSAGE. PLEASE DO NOT REPLY.

Please read instructions on reverse before completing form. Form Approved, OMB No. 2070-0060

EPA

United States
Environmental Protection Agency
Washington, DC 20460

☐ **Registration**
☒ **Amendment**
☐ **Other:**

OPP Identifier Number

Application for Pesticide - Section I

1. Company/Product Number	2. EPA Product Manager	3. Proposed Classification
11556-151	Venus Eagle	☒ None ☐ Restricted
4. Company/Product (Name)	PM#	
Advantage II Small Cat	1	

5. Name and Address of Applicant *(Include ZIP Code)*
Bayer HealthCare LLC, Animal Health Division
PO Box 390
Shawnee Mission, KS 66201

☐ *Check if this is a new address*

6. **Expedited Review.** In accordance with FIFRA Section 3(c)(3)(b)(I), my product is similar or identical in composition and labeling to:
EPA Reg. No. _____
Product Name _____

Section - II

☒ Amendment – Explain below.
☐ Resubmission in response to Agency letter dated _____
☐ Notification - Explain below.
☐ Final printed labels in response to Agency letter dated _____
☐ "Me Too" Application
☐ Other - Explain below

Explanation: PRIA ACTION (R340- Amendment requiring data review in RD.) See attached for more detail.
Enclosed for Agency acceptance is revised draft labeling for the subject product, dated 06/25/12, proposing to amend the registration of Advantage II Small Cat to add the use of the product for flea control on an additional companion animal species – ferrets.

Section - III

1. Material This Product Will Be Packaged In:

Child-Resistant Packaging	Unit Packaging	Water Soluble Packaging	2. Type of Container
☐ Yes* ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Metal ☐ Plastic ☐ Glass ☐ Paper ☐ Other (Specify)
**Certification must be submitted*	If "Yes" Unit Packaging wgt. / No. per container	If "Yes" Package wgt. / No. per container	

3. Location of Net Contents Information	4. Size(s) Retail Container	5. Location of Label Directions
☐ Label ☐ Container		☐ On Label ☐ On labeling accompanying product

6. Manner in Which Label is Affixed to Product ☐ Lithograph ☐ Paper glued ☐ Stenciled ☐ Other _____

Section - IV

1. Contact Point *(Complete items directly below for identification of individual to be contacted, if necessary, to process this application)*

Name	Title	Telephone No. (Include Area Code)
Douglas A. Spilker, Ph.D.	Manager, EPA Regulatory Affairs	913-268-2751

Certification

I certify that the statements I have made on this form and all attachments thereto are true, accurate and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine or imprisonment or both under applicable law.

6. Date Application Received **(Stamped)**

2. Signature	3. Title	5. Date
Douglas A. Spilker	Manager, EPA Regulatory Affairs	27 June 2012
4. Typed Name: Douglas A. Spilker, Ph.D. (doug.spilker@bayer.com)		

EPA Form 8570-1 (Rev. 8-94) Previous editions are obsolete White- EPA File Copy (original) Yellow- Applicant Copy

ATTACHMENT FOR
APPLICATION FOR PESTICIDE REGISTRATION
June 27, 2012

Advantage II Small Cat (EPA Reg. No. 11556-151)

Please find enclosed for the Agency's review and acceptance revised draft labeling, dated 06/25/12, for the subject product. Please note that the enclosed proposed label for use on ferrets is a revision of a pending draft label, text dated 3/26/12, that was submitted in response to the EPA "Implementation of Label Changes to Pet Spot-On Products" document, dated 9/30/11.

PRIA Determination: Since this product, Advantage II Small Cat, can already be used on cats, another companion animal, this amendment of the label is not considered a new use. This amendment does require data review within RD (efficacy and companion animal safety studies) and therefore has been determined to be classified as R340.

The proposed use pattern on ferrets (see highlighted copy of label; enclosed) includes:

1. Inclusion of a minimum weight and age restriction statement for ferrets, based on the companion animal safety study. The protocol for the ferret companion animal safety study was reviewed by the Agency (see Decision No. 449726).
2. Inclusion of a "Side Effects" section based on observations from the companion animal safety studies and the efficacy study.
3. As requested in email from the Agency (A. Metzger to D. Spilker, 2/29/12), inclusion of a statement to limit application to one tube per treatment, regardless of animal size or species.
4. Addition of a separate PRODUCT INFORMATION section for use on ferrets. Flea control on ferrets is supported by the enclosed efficacy report, and by previously submitted studies conducted with Advantage II used to support flea control on cats.
5. Other "word-smithing" to appropriately incorporate the ferret usage in certain other areas of the label.

If there are any questions regarding these revisions, please contact us immediately [doug.spilker@bayer.com ; (913)-268-2751].

48880900

Bayer HealthCare
Animal Health

Via Federal Express

June 27, 2012

Document Processing Desk (REGFEE)
Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Attention: Ms. Venus Eagle/PM01
Registration Division (7505P)

Subject: Advantage II Small Cat (EPA Reg. No. 11556-151)
Proposal to add use on ferrets – **PRIA Category R340**

Bayer HealthCare LLC
Animal Health
P.O. Box 390
Shawnee Mission, KS 66201-0390

Dear Ms. Eagle:

Please find enclosed an application to amend the registration of Advantage II Small Cat to add the use of the product for flea control on an additional companion animal species – ferrets. Since this product can already be used on cats, another companion animal, this amendment of the label is not considered a new use.

Also enclosed are the respective companion animal safety and efficacy studies to support the safe use of this product on adult and pediatric (kits) ferrets. The titles of the reports may refer to the subject product as "M880 Insecticide," the previous code name for the product, but the formulation is the same as Advantage II Small Cat.

We also bring to your attention that we submitted an executive summary of the two companion animal safety studies (Bayer Study Nos. 152.544 and 152.545) to the Agency pursuant to the reporting requirements of FIFRA 6(a)(2); copy enclosed.

If you have any questions, please do not hesitate to call me at 913-268-2751.

Sincerely,

Douglas A. Spilker, Ph. D.
Manager, EPA Regulatory Affairs
Doug.Spilker@Bayer.com

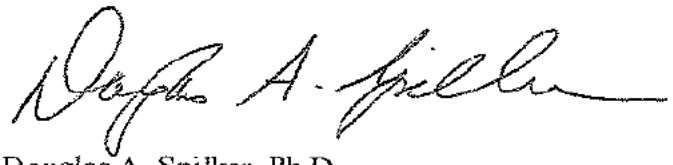
Enclosures:

1. Copy of PRIA payment
2. Application with attachment
3. 6(a)(2) letter with executive summary, dated 2/24/12
4. Email of 2/29/12 (A. Metzger to D. Spilker)
5. Advantage II Small Cat Draft Label, dated 6/25/12 (3 copies)
6. Advantage II Small Cat Draft Label, dated 6/25/12 (highlighted; 1 copy)
7. Bayer Report No. 33973 (3 copies)
8. Bayer Report No. 38333 (3 copies)
9. Bayer Report No. 38334 (3 copies)

Transmittal Document

1. Name and Address of Submitter

Bayer HealthCare LLC
Animal Health Division
Box 390
Shawnee Mission, Kansas 66201-0390



Douglas A. Spilker, Ph.D.
Manager, EPA Regulatory Affairs
(913) 268-2751

2. Regulatory Action in Which this Package is Submitted

Propose new use of Advanatge II Small Cat (EPA Reg. No. 11556-151) for use on ferrets.

3. Transmittal Date

June 27, 2012

4. List of Submitted Studies:

MRID No.	Volume		
48880901	1	-	"Pilot General Safety Evaluation of M880 Insecticide on Pediatric Ferrets," Study No. 152.544, Bayer Report No. 38333, 87 pp.
48880902	2	-	"Evaluation of the General Safety of M880 on 10-Week-Old Ferrets," Study No. 152.545, Bayer Report No. 38334, 201 pp.
48880903	3	-	"Laboratory Evaluation of the Efficacy of *Advantage II for Small Cats* (9.1% Imidacloprid + 0.46% Pyriproxyfen) for the Treatment and Control of Cat Fleas (*Ctenocephalides felis*) on Ferrets," Study No. 152.475, Bayer Report No. 33973, 23 pp.

Pages 91-92 - *Confidential Statements Pages 272-273 - *Confidential Statements of Formula may be entitled to confidential treatment*